Chapter

27 Antineoplastic Agents

1. INTRODUCTION

The past three decades have witnessed a remarkable revolution in the field of tumour chemotherapy. A spectacular wealth of basic knowledge with regard to molecular and cellular biology, better understanding of mechanisms of cellular division, tumour immunology, fundamental factors involved in both viral and chemical carcinogenesis and above all the improved investigative techniques have ultimately led to the introduction of a substantial number of newer **antineoplastic agents.**

A few years ago significant palliative results were obtained by chemotherapy in a number of human neoplasma. Today it is, however, possible to list at least certain neoplastic diseases that can be associated with a normal life expectancy after treatment with drugs alone or in combination with other modalities. These neoplasms essentially include : carcinoma in women, acute leukemia, Burkitt's lymphoma, Ewing's sarcoma, retinoblastoma in children, lymphosarcoma, Hodgkin's disease, rhabdomyosarcoma, mycosis fungoides and testicular carcinoma.

A **neoplasm,** or **tumour** is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissue and continues in the same manner after cessation of the stimuli which have initiated it.

A **malignant tumour** grows rapidly and continuously, and even when it has impoverished its host and source of nutrition, it still retains the potentiality for further proliferation. Besides, malignant tumours invade and destroy neighbouring tissues and possess no effective capsule, a malignant tumour readilty ulcerate and tend sooner or later to disseminate and form metastases.

The **causation of neoplasms** are many, for instance : the *genetic factors e.g.*, retinoblastoma is determined by a Mendelian dominant factor and so are the multiple benign tumours ; the *chemical carcinogens e.g.*, arsenic, soot, coal tar, petroleum lubricating oil ; the *polycyclic hydrocarbon carcinogens e.g.*, 1, 2, 5, 6-dibenzanthracene, 3, 4-benzpyrene.

There has been a tremendous growth in different aspects of cancer research, cancer chemotherapy *vis-a-vis* a better understanding of the intricacies of the '**tumour biology**' that has ultimately led to not only the legitimate evolution but also the explicite elucidation of the probable mechanisms of action for the **antineoplastic agents.** In fact, the various strategies involved to augment the speedy as well as meaningful progress in the develoment of **antineoplastic agents** may be accomplished as follows :

(*a*) Fundamental basis for the more rational approach in the design of newer drugs,

(*b*) Large collaborative investigations, concerted integrated research based on recent developments and advances in the clinical techniques, and

(*c*) Combination of such privileged advantages with improved preliminary screening methodologies.

As on data nearly ten differnet types of '**neoplasms'** may be '**cured**'* with the aid of chemotherapy in patients quite satisfactorily, namely : leukemia in children, Hodgakin's disease, Burkitt's lymphoma, Ewing's sarcoma, choriocarcinoma in women, lymphosarcoma, mycosis fungoides, rhabdomyosarcoma, testicular carcinoma, and retinoblastoma in children.

It is pertinent to raise a vital question at this point in time—**'why cancer is rather difficult to cure in comparison to other microbial infections'**. One may put forward the following plausible explanations as :

(*i*) Qualitative differences existing between the human and bacterial cells. It is well known that the bacterial cells. possess distinctive cell walls ; besides, the ribosomes also differ entirely from those of '**human cells**',

(*ii*) Quantitative differences do prevail between **normal and neoplastic human cells**, and

(*iii*) Body's immune mechanisms and other host defenses play a vital role in killing bacteria (*i.e.,* bactericidal) plus other susceptible foreign cells ; whereas they are not so prevalent in destroying cancerous cells.

Evidences of quantitative differences do exist in the natural characteristics of *proteins* observed in monitoring various essential pathways which in turn control *three* major operations, namely : (*a*) cell proliferation ; (*b*) cell differentiation ; and (*c*) induction of programmed cell death (*i.e.,* **apoptosis**)—also necessarily catering for much desired '**targets for antineoplastic agents.**** In a situation, whenever the cancerous cells overcome the **'body's suveillance mechanism'**, the chemotherapeutic agents (*i.e.,* **antineoplastic agents**) should be able to destroy, kill and thus erradicate completely each and every residual **clonogenic malignant cell,** since even one cell may refurbish and reestablish the cancerous tumour.

Incidence of Tumors :

The **incidence of tumours** vary from age, sex, geographical, ethnic, environmental, virus, radiation and hormone factors as stated below :

(*a*) **Age Incidence :** *e.g.*, *embryonic mesenchymoma* group originate and disseminate even before birth ; **sarcoma** arises in adolescence ; *carcinoma* takes place after the age of 40 years and increases with advancing years ; *bone sarcoma* occurs between 10-12 years ; *cancer of prostrate* becomes active in old age.

(*b*) **Sex Incidence :** *e.g.,* **post-cricoid cancer** is found 90% in young women ; *cancer of lower part of oesophagus* occurs in elderly men.

(*c*) **Geographical Incidence :** *e.g.*, **nasopharyngeal cancer** is common among Chinese and rare in other races ; **Cancer of mouth and tongue** is common in India ; **Cancer of bladder** is common in Egypt ; **Cancer of liver** is common in Central Africa.

(*d*) **Ethnic Incidence :** *e.g.*, uncircumsised males suffer from **penile carcinoma** and their wives often suffer from **carcinoma of cervix**.

*Cure means-an expectation of normal longevity.

Dorr RT and Von Hoff DD (eds) : **Cancer Chemotherapy Handbook, Appleton and Lange, Norwalk CT, 2nd edn., pp3-14, 1994.

(*e*) **Environmental Incidence :** *e.g.*, **bronchogenic carcinoma is** found mostly among cigarette smokers and people in industrialised areas due to air pollution and asbestos fibre inhalation.

(*f*) **Virus Incidence :** *e.g., polyoma virus* when gets in contact with host cell, it destroys it by feeding on it and releasing its DNA. Consequently, when this DNA gets in contact with host DNA, a new DNA with different genetic (genotype) material is formed. As this genotype is different, it grows differently from the normal cell leading to cancerous cells.

(*g*) **Radiation Incidence :** *e.g.*, **osteosarcoma** is found in subjects handling paints containing radium ; radiologists mostly suffer from leukemia.

(*h*) **Hormone Incidence :** *e.g.*, **breast cancer** in mice is produced by administration of large doses of *oestrogens.*

1.1. Chemotherapeutic Intervention

The various aspects of **chemotherapeutic intervention** may be discussed in an elaborated manner under the following defined categories, such as :

(*i*) Phase specificity,
(*ii*) Tumour selectivity and response,
(*iii*) Determinants of sensitivity and selectivity,
(*iv*) Requirements for 'kill',
(*v*) Combination chemotherapy,
(*vi*) Log cell-kill principle, and
(*vii*) Drug resistance.

Each of the above aspects shall now be treated individually in the sections that follows :

1.1.1. Phase Specificity

Broadly speaking the '*antineoplastic drugs*' may be categorized under *two* heads, namely :

(*a*) **Phase nonspecific drugs.** These drugs have an ability to act on the cell throughout the cell-cycle, and

(*b*) **Phase specific drugs.** The drugs act **preferentially** during one or more of the nonresting phases. In other words, they prove to be '*absolutely ineffective*' when delivered to the cell specifically during the *wrong phase.*

Figs. 27.1 and 27.2 illustrate the **cell-life cycle** and the **cell-cycle specificity** respectively as given below :

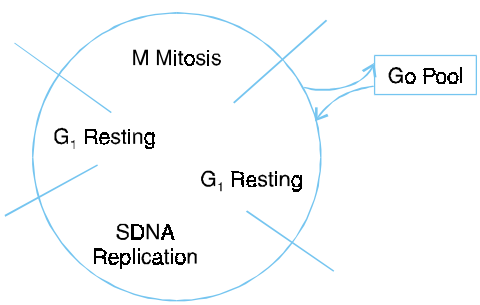


Fig. 27.1 Cell-Life cycle.

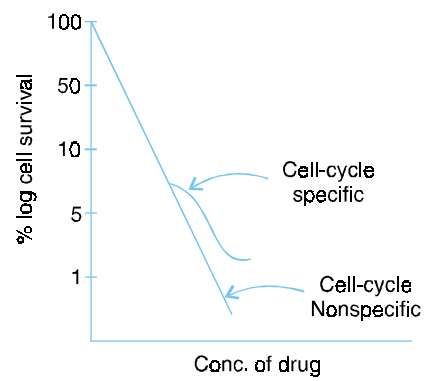


Fig. 27.2. Cell-cycle specificity.

Fig. 27.1 evidently shows a circular pictorial model actually obtained for the clockwise progression of the cell-cycle. In actual practice, however, both the duration of individual phase in the cell cycle alters appreciably guided by the cell type, and also within a single tumour. Following are some of the '**typical durations'**, for instance :

S—DNA : replication phase = 10-20 hours ;

G_2—Resting phase = 2-10 hours ;

G_1—Resting phase = highly variable due to another phase ;

M—Mitosis phase = 0.5 – 1 hours ;

G_0—Pool = Cell not active during cell division.

Salient-Features of Antineoplastic Drugs

These are as follows :

(*i*) Block the **biosynthesis** or **transcription of nucleic acids** to check cell-division through direct interference with mitotic spindles,

(*ii*) Both **mitosis phases** and cells that are engaged in **DNA-synthesis** are found to be highly susceptible to these **antineoplastic agents**, and

(*iii*) In the resting state the **not-so-fast growing tumours invariably possess good number of cells**.*

Fig. 27.2 explicitely represents the overall effects of **antineoplastic agents** upon the cell survival which is exponentially related to dose. Now, if a plot is made between **log cell survival** along the Y-axis and the **drug concentration** along the X-axis one would get a '**straight line'**. Nevertheless, these drugs usually display their cytotoxicity irrespective of the **cell-cycle-phase** ; and, hence, are known as the '**non-cell cycle phase specific drugs'.** Importantly, such other drugs *viz.*, **mitotic inhibitors** and **antimetabolites**, that particuarly act at one phase of the cell cycle only, normally display a distinct **plateau** soonafter a **preliminary low-dose exponential region**.

1.1.2. Tumour Selectivity and Response

It has been duly observed that paricularly for '**phase-specific drugs**' (see Section 1.1.1.*b*), the probability apprehended for a lethal action on a cancerous tumour cell (or nomal cell) is usually directly proportional to the actual percentage of time consumed in the '*vulnerable phase.*' In other words, one may ascertain that the real percent of time spent specifically in the vulnerable phase appears to be an important '**determinant factor**'for the susceptibility of tumours belonging to different cell types. Not withstanding to any particular growth phase one may safely generalize that such tumours having a large growth fraction one prone to chemotherapy in comparison to those having a low fraction ; and this constitutes a very ideal and equally important percept.

Examples : (*a*) **Cancerous tumors** having high growth fractions which are found to give adequate response to chemotherapy are, namely : **Hodgkin's disease**, **Burkitt's lymphoma***, **Wilm's tumour**, **acute leukemia in children**, **choriocarcinoma****, **chronic myelogenous leukemia****, **lymphocytic leukemia**, and **breast cancer**.

(*b*) **Neoplasms** (*i.e.*, **malignant tumours**) which afford a very poor response are, for instance : carcinoma of the GI-tract, malignant melanoma, and tumours of the uterus and cervix.

*Mackillop WJ *et. al. J. Natl. Cancer Inst.*, **70** : 9, 1983.

**These tumours are now considered curable to a great extent.

Salient Features. Following are some of the cardinal salient features with regard to tumour selectivity and response :

(1) Efficacy of antineoplastic drugs is increased significantly in early treatment of *newly developed small cancerous tumours* having relatively higher growth fractions.

(2) Most effective **antineoplastic drug** should invariably be expected to be of such kind which is rather specific to the phase with the longest duration *e.g.*, **S-DNA** : **replication phase** (10-20 hours), and **G_2-resting phase** (2-10 hours).

(3) Recently, investigation of the possibility of *synchronizing cancerous tumor cells* is gaining momentum so that most likely **all cells are in the same phase of the cycle.** In case, such in '*ideal situation*' may be accomplished then :

(*a*) Cancerous tumor might become more vulnerable to the suitable drugs administered at the right-time, and

(*b*) Therapeutic index of the '**drug**' may be enhanced appreciably.

(*c*) *Synchronization* is achieved by a *holding pulse* of a **mitostatic drug** which essentially holds the cells in a specified phase till such time the *out-of-phase* cells also come into that phase.

(*d*) Sudden or planned discontinuation of the '**synchronizing antineoplastic drug**' at the same time releases the cancerous cells to resume their own specific cycle *i.e.*, all commencing afresh from the same phase.

(*e*) Combination chemotherapy, the **antineoplastic drugs** are frequently administered in a particular '*sequence*', instead of simultaneously ; however, in usual practice the **first-administered antineoplastic drug** invariably stands for a **synchronizing drug**.

1.1.3. Determinants of Sensitivity and Selectivity

There are certain pivotal factors that essentially help in determining the *selectivity* of **antineoplastic drugs** required for some definite cell-types. Besides, the actual demand for *various nutrients* also varies significantly amongst different tumor types, as do they differ frequently between the **tumor cells** and the **normal cells.**

Example. A plethora of malignant tumors of need much more **asparagine** (a nonessential amino acid) in comparison to normal cells ; therefore, if by any manner the plasma asparagine gets destroyed (enzymatically), the cancerous tumor cells in turn are selectively *starved* to death.

It has been observed duly that some '**drugs**' either get metabolized in the *liver* or the *peripheral cells* thereby the various cell types substantially differ in their respective ability to metabolize these drug substances.

Example. Bleomycin—an **antineoplastic drug** usually gets metabolized much less in the *susceptible tumor cells* in relation to other cells, thereby allowing distinctly higher local concentrations. In addition to this there are a host of other antineoplastic drugs which are converted to the *active metabolites* by the aid of the prevailing '**target-cells**' (also termed as **'lethal synthesis'**) ; and the ensuing differences in the conversion rates ultimately contribute directly to **selectivity.**

Degree of variance in penetrance also account for certain critical apperent differences amongst the antineoplastic drugs.

Example. (*i*) **Neoplasms in the CNS** are more effectively curable by lipid-soluble drugs than the water-soluble ones,

(*ii*) Some drugs exhibit *greater active transport* into cancerous tumor cells than into normal cells,

(*iii*) Certain drugs show differences in '**outward transport**' as well,

(*iv*) Selectivity is also governed by tumor-cell attacking **killer T-cells, suppressor T-cells**, and **blocking factors from B-cells** which specifically guard and protect some cancerous cells from the prevailing immune attack, and

(*v*) Generally, the immune cells are established to be the most suppressed ones ; and thus two situations may arise : *first*, **antineoplastic drugs** which augment response to malignant cells and *secondly*, which antagonize it squarely.

1.1.4. Requirements for 'Kill'

Ideally, a remission (*i.e.*, reduction in intensity) normally may be accomplished with a '**kill**' ranging between 90-99% of the neoplastic cells. Interestingly, a '**kill**' amounting to 99% is supposed to leave a bear minimum of 107-108 surviving neoplastic cells to continue tumor growth, and consequently the remission would stay on 3-4 doubling times only. From these observations one may safely infer that such neoplasms against which the immune-system is absolutely ineffective, a **100% kill'** is not only a prerequisite but also necessary to cause a '**true cure**'**.**

1.1.5. Combination Chemotherapy

It has been amply tested, tried and established beyond any reasonable doubt that one may enhance the '**percent of kill'** by employing the **combination therapy** of two or even more antineoplastic agents judiciously. Of course, the usage of **radiation therapy** can also be effectively used with drugs. In reality, there exits *four* cardinal factors that may optimize such '**combinations**', namely :

(*a*) Each component drug should have certain **degree of efficacy** by itself.

(*b*) Each component drug must have an altogether different mechanism of '**cytotoxic profile'** and, preferably, command **phase specificity**.

(*c*) Each component drug should have a distinct and different **spectrum of toxicity** in comparison to the other components, so as to avoid specifically any overwhelming toxicity of a given type.

(*d*) The '**mechanism of resistance**' to each component must be invariably different to that of the other components.

1.1.6. Log Cell-Kill Principle

It has been well-defined that the efficiency of **anitneoplastic drugs** may be characterized by their inherent **log cell-kill index.** In other words, the **negative log of the fraction** of the cancerous tumor cell population which essentially survives a *single-course of treatment.*

Example. A **neoplastic drug** that eventually kills 99.9% of the malignant tumor cell population, *i.e.*, leaves 0.0001 (or 1/104) of the population is usually termed as a **4-log drug** ; whereas, a second drug which kills 99.9% is known as a **3-log drug.**

However, the **log cell-kill index** represents a very thin (tenuous) number, but it definitely serves a tremendous usefulness in rightly predicting the effects of combinations which essentially fulfil criteria (*a*) and (*b*) above (Section 1.1.5). Thus, the very close predicted effect of a combination is usually accomplished by the simple addition of the various indices obtained from the component drugs.

Example. Theoretically, a **4-log drug** together with a **3-log drug** must provide ordinarily a **7-log combination** *i.e.*, almost kills 99.99999% or leaves 1/107 of the population. Now, at this juncture a 3**rd** drug which essentially kills 99% (**2-log-drug**) may further minimize the remaining population to the extent of 1/109, that ultimately comes close to the complete eradication of a cancerous tumor noticed at an early stage.

1.1.7. Drug Resistance

It has been observed that there are certain tumour populations that seem to be heterogeneous in nature by the time the cancerous tumor is discovered after the usual **'biopsy examination' ;** whereas a few of the cells being resistant to some **antineoplastic agents** right at the very outset of the recommended treatment. The said findings hold good for certain well-established organs of the human body, such as : colon, jejunal, adrenal, kidney and liver carcinomas. A maximum of *four* different malignant cell-types have been duly recognized and identified in a single tumor.

It is, however, pertinent to mention here that a certain degree of resistance appears to be acquired in much as the same manner as in **microbial resistance**, such as :

(*a*) resistance granting '**genetic change**' taking place during treatment, and

(*b*) resistant '**daughter cells**' consequently proliferate in the prevailing environment of the antineoplastic agent.

In a nut shell, irrespective of the actual cause, the prevailing resistance invariably negates the usefulness of an **antineoplastic agent** to an appreciable extent.

In fact, there are **ten** different mechanisms of resistance that have been duly identified, namely :

(*i*) Complete loss of the '**transport system**' required essentially for the permeation of the drug into the tumor cell *e.g.*, **methotrexate**.

(*ii*) Disappearance of the enzyme necessary for the intratumor **lethal systhesis** of an essential active metabolite.

(*iii*) An enhancement in the production of the **target enzyme** *e.g.*, **methotrexate**.

(*iv*) Retardation in the *affinity for* or the **quantum of the target enzyme** *e.g.*, **methotrexate**, **fluorouracil** and **topoisomerase inhibitors**.

(*v*) **Pleiotropic drug-resistance** *i.e.*, an enhancement in the outward active transport of the antineoplastic drug, whereby the effective intracellular concentrations cannot be accomplished or maintaned.

(*vi*) **Over expression of metallothionine** in resistance to **Pt-containing drug** and some **alkylating antineoplastics**.

(*vii*) **Formation of antibodies** *e.g.*, **interferons**.

(*viii*) **Membrance of antibodies** which essentially afford resistance to natural **killer (NK) cells**.

(*ix*) Enhance **glutathione synthesis** in malignant cells being treated with anthracyclinedione cells.

(*x*) Repair of potentially **lethal DNA damage**.

2. CLASSIFICATION

Antineoplastic agents are classified under the following *seven* categories, namely :

(*i*) Alkylating Agents
(*ii*) Antimetabolites
(*iii*) Antibiotics
(*iv*) Plant products
(*v*) Miscellaneous compounds
(*vi*) Hormones
(*vii*) Immunotherapy.

2.1. Alkylating Agents

Alkylating agents are chemically reactive compounds that combine most readily with nucleophilic centres a fully saturated carbon atom of the alkylating group becoming attached to the nucleophile.

The term '**alkylating agents**' is applied to compounds which, in a sense, *alkylate* the substance with which they react, by joining it through a **covalent bond**, although a strong polar bond is not excluded from this general definition. Any '**antineoplastic agent**' whose activity is explained by such a mechanism is called an **alkylating agent**.

These are further sub-divided into *four* categories, namely :

(*i*) Mustards
(*ii*) Methanesulphonates
(*iii*) Ethylenimines
(*vi*) Nitrosoureas

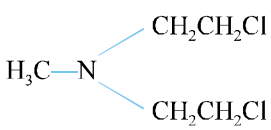
2.1.1. Mustards

After the discovery of the **antileukemic activity of mustard gas** : (Cl CH_2 $CH_2)_2S$ Bis-β-chloroenthyl sulphide (**Mustard Gas**) in human being, its clinical application for the treatment of neoplasms could not be persued further due to its high toxicity, low solubility in water, oily nature and blister-producing properties.

Nitrogen mustards were selected for the clinical application for the treatment of neoplasms because they presented fewer problems in handling, besides their respective hydrochlorides and other salts are generally stable solids having low vapour pressure and high solubility in water.

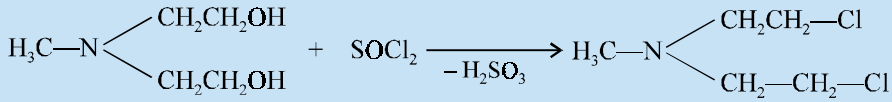
A few important **nitrogen mustards** used as **antineoplastic agents** are discussed below, for instance : **Mechlorethamine hydrochloride**, **Mephalan**, **Cyclophosphamide** and **Chlorambucil**.

A. Mechlorethamine Hydrochloride USAN



2, 2-Dichloro-N-methyldiethylamine hydrochloride USP ; Mustine Hydrochloride BP ; Mustargen(R) (Merck Sharp & Dohme) ;

Synthesis



2, 2′-(Methylimino) diethanol Thionyl chloride Mechlorethamine Hydrochloride

Chlorination of 2, 2′-(methylimino) diethanol with thionyl chloride gives rise to the desired official compound, with the elimination of sulphurous acid.

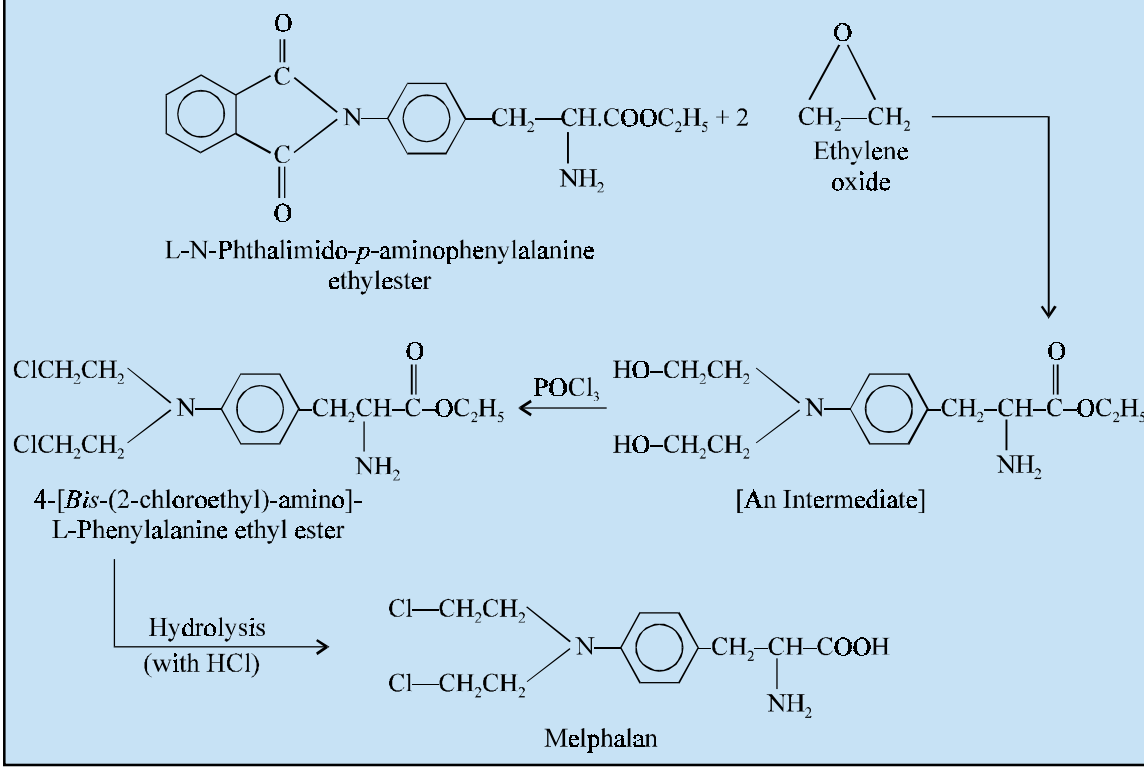
It is effective in Hodgkin's disease. Usual practice is to administer **mechlorethamine** with other **antineoplastic agents** such as **vincristine**, **prednisone** etc. It is the drug of choice for the treatment of mycosis fungoides and lymphomas.

Dose. *Single doses of 400 mcg per kg body weight or a course of 4 daily doses of 100 mcg per kg are normally administered by iv injection in a strength of 1 mg per ml in sodium chloride injection.*

B. Melphalan **USAN,**

4-[Bis (2-chloroethyl) amino]-L-phenylalanine ; L-Mustard ; L-Sarcolysin ; USP ; BP ;
Alkeran(R) (Burroughs Wellcome) ;

Synthesis

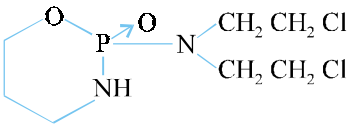


L-N-Phthalimido-*p*-aminophenylalanine ethyl ester when reacted with ethylene oxide yields an intermediate which on treatment with phosphorus oxychloride gives rise to 4-*Bis*-(2-chloroethyl)-amino-L-phenylalanine ethyl ester. This on hydrolysis with hydrochloric acid offers the desired compound.

Melphalan is very effective in preventing the recurrence of cancer in premenopausal women who have undergone radical mastectomy.

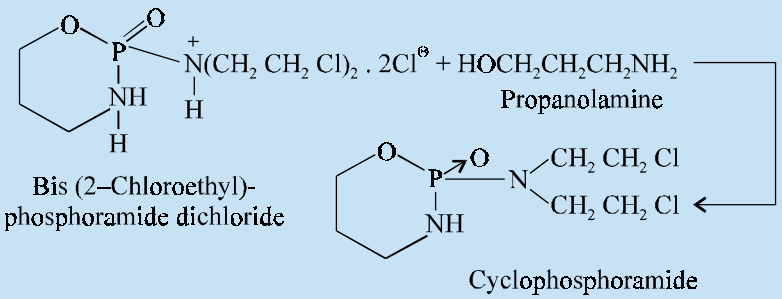
Dose. *Oral, 150 mcg per kg body weight daily for 4 to7 days, combined with prednisone 40-60 mg dialy ; 250 mg per kg daily for 4 to 5 days ; or 6 mg daily by 2 to 3 weeks.*

C. Cyclophosphamide BAN, USAN,



N, N-Bis (2-chloroethyl) tetrahydro-2H-1, 1, 3, 2-oxazaphosphorin-2-amine-2-oxide ; BP ; USP ; Cytoxan(R) (Mead-Johnson) ;

Synthesis

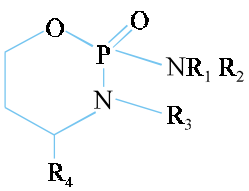


It is prepared by the interaction of bis-(2-chloroethyl) phosphoramide dichloride with propanolamine.

Cyclophosphamide is effective against acute leukemia, chronic lymphocytic leukemia and multiple myeloma. In combination with other chemotherapeutic agents it is found to cause radical cure in acute lymphoplastic leukemia in children and also in Burkitt's lymphoma. It has a positive advantage over other alkylating agents because of its activity both parenterally and orally besides its tolerance over prolonged periods in divided doses.

Dose. *Intitial, adult dose of 40-50 mg per kg, given intravenously in divided doses over 2 to 5 days ; Children : 2-8 mg per kg daily iv injection.*

Cyclophosphamide is one of the most useful antineoplastic agents and substitution at C-4 position has led to **4-phenyl cyclophosphamide** (*a*) and **4-methyl cyclophosphamide** (*b*) The most commonly used analogues of **cyclophosphamide** are **Ifosfamide** (*c*) and **Trofosfamide** (*d*) :



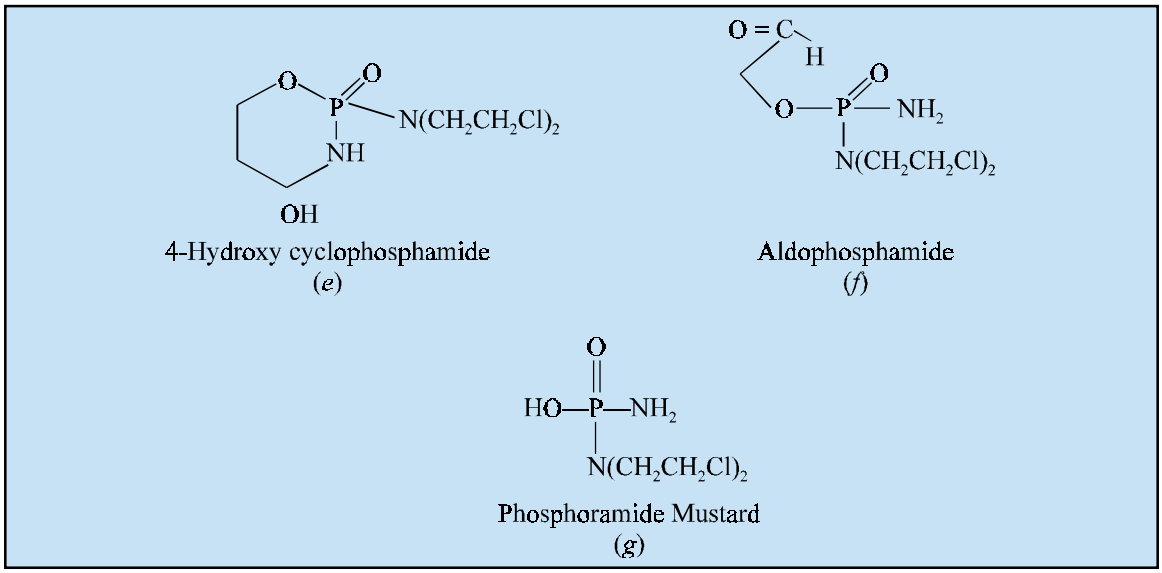
(*a*) : $R_1 = R_2 =$ —$CH_2\ CH_2\ Cl$; $R_3 = H$; $R_4 = C_6H_5$;

(*b*) : $R_1 = R_2 =$ —$CH_2\ CH_2\ Cl$; $R_3 = H$; $R_4 = CH_3$;

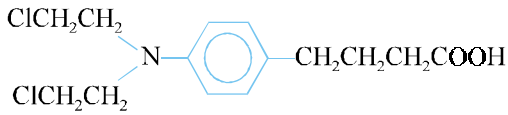
(*c*) : $R_1 = R_3 =$ —$CH_2\ CH_2\ Cl$; $R_2 = R_4 = H$;

(*d*) : $R_1 = R_2 = R_3 =$ —$CH_2\ CH_2\ Cl$; $R_4 = H$:

Enzyme catalyzed oxidation of **cyclophosphamide** yields **4-hydroxy cyclophosphamide** (*e*) and subsequent formation of **aldophosphamide** (*f*) that leads to **phosphamide mustard** (*g*) which is considered to be the ultimate alkylating agent.

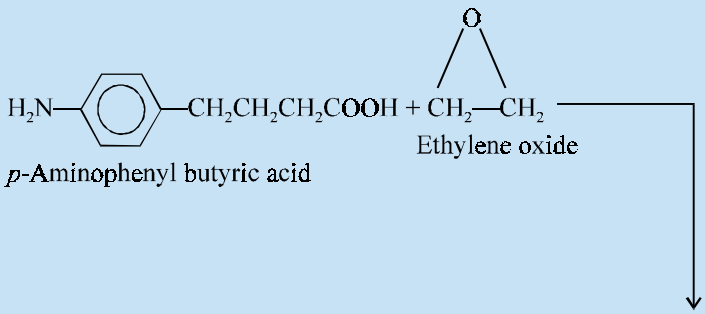


D. *Chlorambucil* USAN



4-[*p*-Bis (2-chloroethyl) amino] phenyl] butyric acid ; Chloraminophene ; USP ; Leukeran(R) (Burroughs Wellcome) ;

Synthesis



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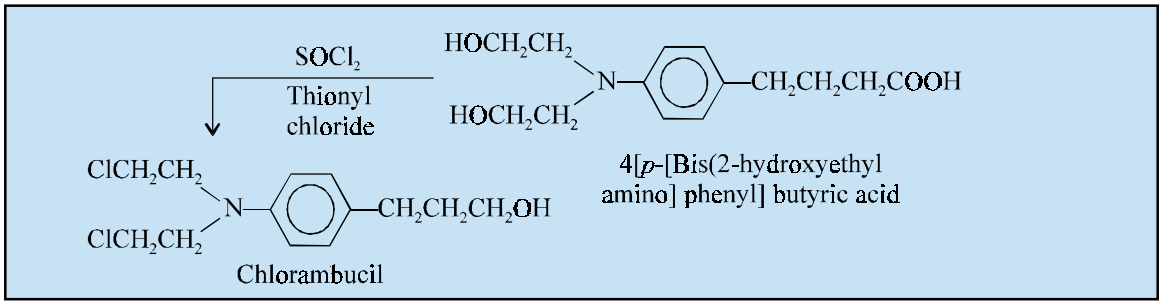


Chlorambucil is prepared by treating *p*-aminophenyl butyric acid with enthylene oxide to yield 4-[*p*-[Bis (2-hydroxyethyl) amino] phenyl] butyric acid which on chlorination with thionyl chloride offers the desired product.

It is indicated in treatment of Hodgkin's disease, lymphosarcoma, primary microglobulinemia and chronic lymphocytic leukemia. It has an edge over other nitrogen mustards because of its least toxicity and slowest activity.

Dose. *Usual, oral, 100 to 200 mcg per kg body weight daily (usually 4 to 10 mg as a single daily dose) for 4 to 8 weeks.*

2.1.1.1. Mechanism of Action

The mechanism of action of the drugs described under Section 2.1.1 shall be dealt with in the sections that follows :

2.1.1.1.1. Mechlorethamine Hydrochloride

The β-chloroethyl moieties lose Cl^- ions to generate carbonium and azardium (ethylerimonium ions), that are found to be extremely reactive ; and are capable of alkylating many biologically vital chemical moieties. It has been observed that in DNA they alkylate guanine moieties ; if one arm alkylates **one guanine group** and the second arm another guanine on the opposing strand of prevailing double-stranded DNA, the DNA turns into irreversibly cross-linked. It ultimately gives rise to inhibition of mitosis, besides causing chromosomal breakage. Importantly,some undifferentiated germinal cells are nonproliferative and hypertrophied during exposure to the '**drug**', whereas the rather more differentiated germinal cells usually disintegrate. Besides, some malignant growths, specifically of the lymph modes and bone marrow, seem to be more sensistive to the drug in comparison to the normal more slowly proliferative tissues.

2.1.1.1.2. Melphalan

The '**drug**' serves as a primary immunosuppressive drug. It is found to be well absorbed *via* the oral route, being also equally efficacious as administered by the IV route. The **'drug'** gets transformed into active metabolites in probably all tissues. The elimination half-life ranges between 1 to 3 hours.

2.1.1.1.3. Cyclophosphamide

The '**drug**' behaves unlike other β-chloroethylamino alkylators, and hence fails cyclize rapidly to the corresponding active ethylene imonium form unless and until activated by the hepatic enzymes. Importantly, the liver is protected by the further metabolism of activated metabolites into the corresponding inactive end products. Therefore, the '**drug**' is fairly stable in the GI-tract, well tolerated, and quite efficacious both by the oral and parenteral routes. It fails to produce any sort of '*local vasication*', necrosis, phlebitis, or even pain.

It is distributed to the tissues having **volume of distribution** v_d^{ss} more than the total body water. The '**drug**' gets metabolized by the hepatic microsomal system to the corresponding alkylating metabolites, which in turn eventually are duly converted to phosphoramide mustard and acrolein (an aldehyde). However, the relatively high doses readily induce the metabolism of **cyclophosphamide**. The plasma half-life ranges between 4 to 6 hours.

2.1.1.1.4. Chlorambucil

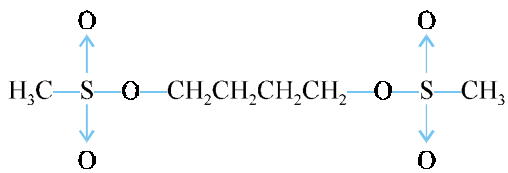
The '**drug**' is one of the slowest-acting and also least toxic currently employed nitrogen mustards. Importantly, its toxicity is manifested chiefly as bone-marrow depression ; however, in the prevailing therapeutic doses it is observed to be fairly moderate and reversible. The '**drug**' gets adsorbed well *via* the oral administration. It generally is degraded extensively *in vivo.* The elimination half-life is nearly 1.5 hour.

2.1.2. Methanesulphonates

From a mechanistic point of view the **methanesulphonates** (or the **methanesulphonate esters**) are specially interesting since the long alkylene chains separating the reductive ester groups virtually exclude the possibility of the formation of reactive intermediate ring structures. Thus, these ester groups constitute a level of direct alkylating ability which need not be mediated by cyclization. The **methanesulphonate ion** is a weakly nucleophilic group which is displaced from carbon by a more strongly nucleophilic group that is present in the biological system acted upon by the drug.

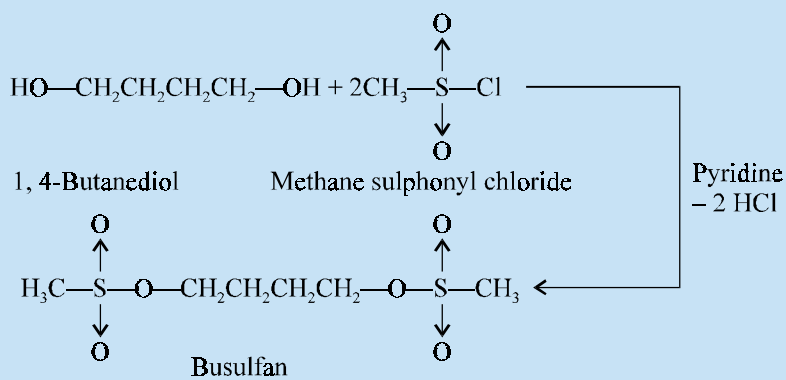
The most important alkylating agent in this group is **Busulfan** :

A. *Busalfan* USAN



1, 4-Butanediol dimethanesulphonate ; 1, 4-Di (methanesulfonyloxy) butane ; BP, USP, Mylearn(R) (Burroughs Wellcome) ;

Synthesis



It is prepared by the interaction of 1, 4-butanediol with two moles of methane sulphonyl chloride in the presence of pyridine, when the final product obtained is recrystallised either from acetone or alcohol. Busulfan is broadly used in the treatment of granulocytic leukemia.

Dose. *For granulocytic leukemia : 60 mcg per kg body weight daily orally, upto a maximum single daily dose of 4 mg and to be continued till the white-cell count falls between 15000 to 25000 per* mm^3.

2.1.2.1. Mechanism of Action

The **mechanism of action** of **busulfan** shall be discussed as under :

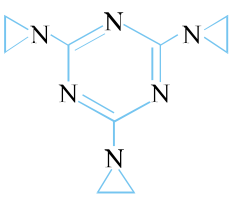
2.1.2.1.1. Busulfan

The '**drug**' is phase nonspecific. It exerts almost negligible action on rapidly proliferative tissues other than the bone marrow. However, at relatively lower dose levels granulo-cytopoesis may be suppressed quite selectively without causing any effect on erythropoises. As the '**drug**' has little effect on lymphopoesis, it is of no value in lymphocytic leukemia and malignant lymphoma. It is found to be not immunosuppressive. Its elimination half-life ranges between 2-3 hours.

2.1.3. Ethylenimines

Clossley first reported the inhibition of experimental tumours in mice by treatment with **triethylene melamine (TEM)** and this resulted in the discovery of another drug **triethylenethio phosphoramide**.

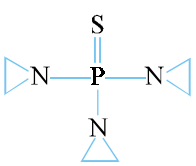
A. *Triethylenemelamine*



2, 4, 6-Tri (1-azridinyl)-S-triazine ; 2, 4, 6-Tris (ethyleneimino)-S-triazine ; 2, 4, 6-Triethyleneimino-1, 3, 5-triazine.

It is used as an adjuvant to radiation therapy of retinoblastoma and injected into the carotid artery. It is used in the palliative treatment of malignant neoplasms.

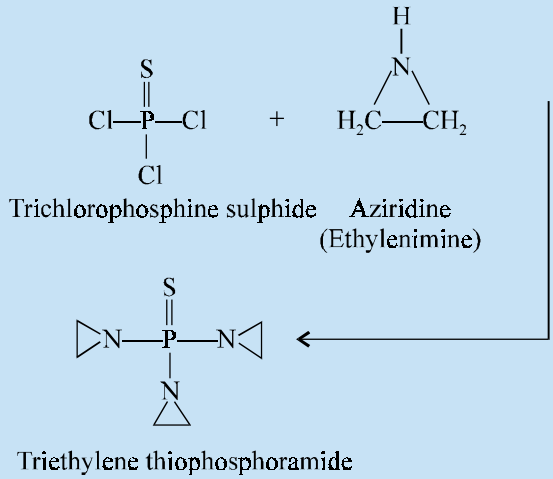
B. *Triethylenethio Phosphoramide* BAN



Tris (1-aziridinyl) phosphine sulphide ; N, N′, N″-Triethylenethio-phosphoramide ; Thiotepa USP ; BP,

Ledertepa(R) (Lederle) ; Thiofosyl(R) (Astra) ;

Synthesis



It is prepared by teating trichlorophosphine sulphide with aziridine and recrystalizing the official product from water.

It is of value in the treatment of carcinoma of breast, ovaries, colon-rectum and rectum. It is also found to be useful in the treatment of malignant lymphomas and bronchogenic carcinomas.

Dose. *Upto 60 mg in single or divided doses may be given by im injection or by instillation in adults and children over 12 years.*

2.1.3.1. Mechanism of Action

The mechanism of action of the '**drugs**' discussed under Section 2.1.3 shall now be treated individually.

2.1.3.1.1. Triethylenemelamine (Tretamine)

Its action and properties are very much akin to **thiotepa** (**triethylenethio phosphoramide**). It happens to cross blood brain barrier (BBB).

2.1.3.1.2. Triethylenethio Phosphoramide (Thiotepa)

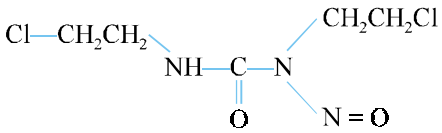
The '**drug**' exerts its action due to its alkylating characteristics. It is extensively metabolized ; and traces of unchanged drug substance are excreted in the urine, along with a large proportion of metabolites. The '**drug**' also crosses the blood-brain barrier (BBB). It has been observed that it undergoes absorption through *serous membrances*, for instance : bladder and pleura, to a certain degree.

2.1.4. Nitrosoureas

Nitrosoureas are having both practical and theoretical interest. They are very highly lipid soluble antineoplastic compounds first synthesized at Southern Research Institute, Birmingham.

A few important members of this category are discussed below, namely : **Carmustine** and **Lomustine**.

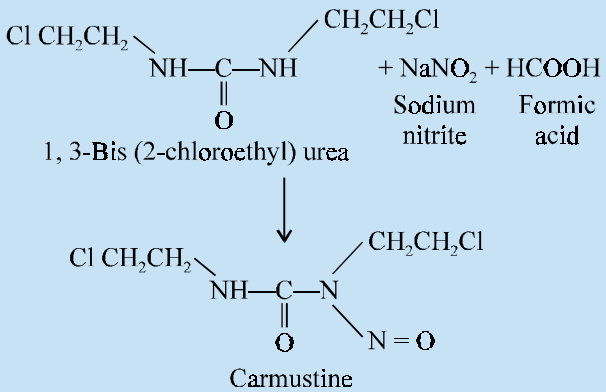
A. *Carmustine* BAN, USAN,



1, 3-Bis (2-chlorethyl)-1-nitrosourea ; BCNU ;

Carmubris(R) (Bristol),

Synthesis

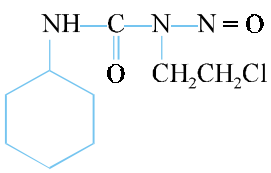


Carmustine may be prepared by interacting 1, 3-bis (2-chloroethyl) urea with sodium nitrite and formic acid. It is a low-melting white powder that undergoes decomposition at 27°C and hence it is supplied as a lypholized powder.

As it possesses the potential to cross the blood-brain-barrier, **carmustine** is employed specifically for brain tumours and other tumours, for instance leukemias, which have metastasized to the brain. A combination of **carmustine** and **prednisone** is used for the treatment of multiple mycloma. As a secondary therapy it is frequently employed in conjunction with other **antineoplastic agents** for lymphomas and Hodgkin's disease.

Dose. *A single dose by IV injection at 100 to 200 mg/m^2.*

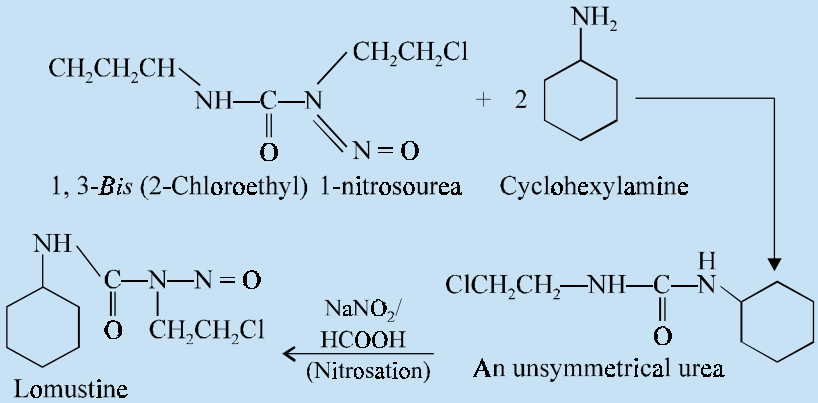
B. *Lomustine USAN*



1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea ; CCNU ;

CeeNU(R) (Bristol) ; CINU(R) (Bristol-Myers) ;

Synthesis



It is prepared by the decomposition of 1, 3-bis (2-chlorethyl)-1-nitrosourea in the presence of two equivalents of cyclohexylamine to yield an unsymmetrical urea which on nitrosation with sodium nitrite and formic acid offers the desired compound.

It is employed effectively in the treatment of primary and metastatic brain tumours. It is also used as secondary therapy in Hodgkin's disease.

Dose. *Usual dosage : 130 mg/m^2 orally every six weeks.*

2.1.4.1. Mechanism of Action

The mechanism of action of the two medicinal compounds described under Section 2.1.4. shall now be treated individually as under :

2.1.4.1.1. Carmustine

The '**drug**' most probably exerts its action due to the ability to cross-like cellular DNA. Thus the very synthesis of both DNA and RNA is ihibited. It is specifically phase nonspecific. The '**drug**' gets metabolized, *via* oral administration, practically 100% as it happens to pass through the liver ; therefore, it should be given IV. It has been observed that after IV administration, its plasma half-life is of rather shorter duration ranging between 3-30 minutes. By virtue of the fact that the '**drug**' has a high lipid solubility profile which renders it to pass through the **blood-brain barrier (BBB)** rather swiftly. Besides, the prevailing concentrations in the **cerebrospinal fluid (CSF)** varies from approximately 50-115% of those in plasma.

2.1.4.1.2. Lomustine

The '**drug**' is a chemical congener of **Carmustine** and, therefore, almost possesses the same mechanisms of action. Just like **carmustine**, it accomplishes maximum concentrations in the CSF ; and, hence, shares with carmustine a **first choice status** for the treatment of *glioblastoma.**

The '**drug**' is found to be well absorbed orally and thereby survives the first pass through the liver to be effective by the oral administration. Besides, it gets distributed evenly amongst the various tissues having a volume of distribution (v_d^{ss}) much higher than the total body water content. However, in the CSF the concentration of metabolites attains almost 150% of that normally present in plasma. It has been observed that the biotransformation usually takes place throughout the body ; the half-life is nearly 15 minutes, and the half-lives of the metabolites are 48 hour.

*A neuroglia (*i.e.*, cells and fibers forming the interstitial elements of CNS) cell tumour.

2.2. Antimetabolites

Antimetabolites are such compounds which essentially prevent the biosynthesis of normal cellular metabolites. They generally possess close structural resemblance to the metabolite which is ultimately antagonized. Thus they have a tendency to unite with the active site, as if they are the actual substrate.

In general, following are the various classes of **antimetabolites** usually employed in the treatment of cancer. They are namely :

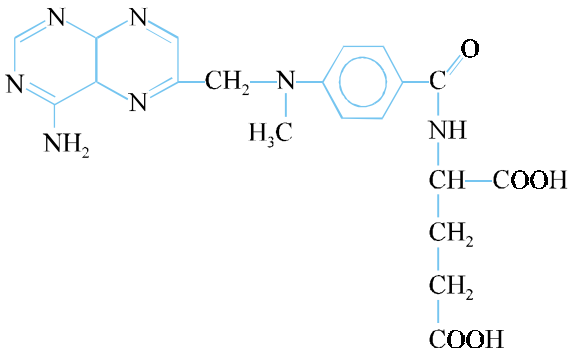
(*a*) Antifolic acid compounds
(*b*) Analogues of Purines
(*c*) Analogues of Pyrimidines
(*d*) Amino acid antagonists

2.2.1. Antifolic Acid Compounds

Antifolic acid compounds are also referred to as '**Antifolics**' or '**Folate Antagonists**' Drugs belonging to this category act by preventing the synthesis of folic acid which is required by the tissues. They bind strongly to **dihydrofolate reductase (DHFR)** thereby inhibiting the conversion of dihydrofolic acid to tetrahydrofolic acid and thus inhibit the synthesis of **purines** and **thymidines**. Antifolics kill cells by **inhibiting DNA synthesis in the S phase of the cell cycle**. Therefore, they are found to be most effective in the log growth phase.

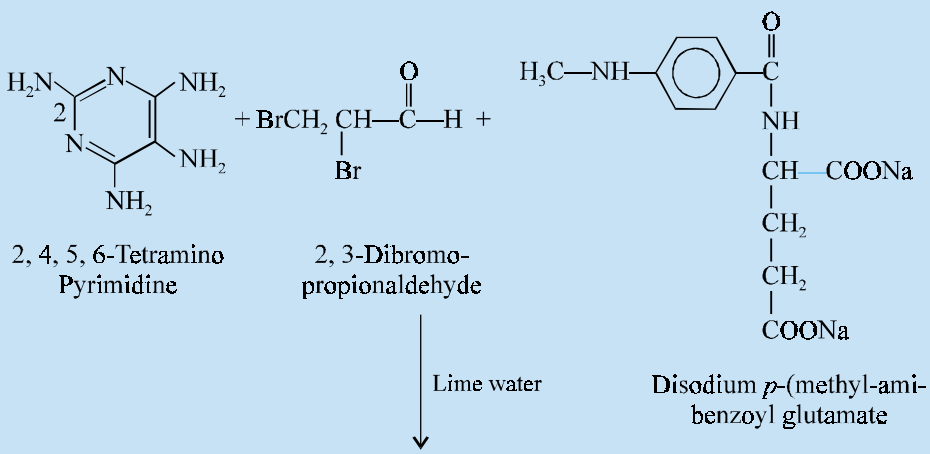
The most important drug in this group is methotrexate.

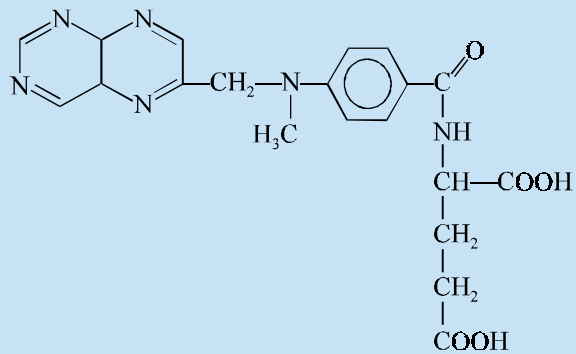
A. *Methotrexate* BAN, USAN, INN



N-[4-[[(2, 4-Diamino-6-pteridinyl) methyl] methylamino] benzoyl]-L-glutamic acid ;
BP (1973) ; USP ;
Amethopterin(R) (Lederle) ;

Synthesis





Methotrexate

It is prepared by treating together 2, 4, 5, 6-tetraaminopyrimidine ; 2, 3-di-bromopropionaldehyde, disodium *p*-(methylamino)-benzoylglutamate, iodine and potassium iodide and subsequently followed by heating with lime water.

It is the first ever **antineoplastic agent** that produced appreciable remissions in leukemia. It is extensively employed for the treatment of acute lymphoblastic leukemia. It is invariably used in combination cheotherapy for palliative management of lung cancer, breast cancer and epidermoid cancers of the head. It is frequently recommended for the treatment and prophylaxis of meningeal leukemia based on its ability to penetrate the central nervous system. It is also of value in choricarcinoma and related trophoblastic tumours of women.

Dose. *For maintenance therapy of acute lymphoblastic leukemia is 15-30 mg per m^2 body surface once or twice weekly, either orally or intramuscularly, with other agents such as mercaptopurine.*

2.2.1.1. Mechanism of Action

The mechanism of action of **methotrexate** shall be discussed as under :

2.2.1.1.1. Methotrexate

The '**drug**' exerts its action by inhibiting the enzyme **dihydrofolate reductase (DHFR)**, and thus prevents effectively the conversion of **deoxyuridylate** to **thymidylate**, that ultimately blocks the synthesis of new DNA required urgently for the cellular replication.

Interestingly, the '**drug**' in doses less than 30 mg/m^2 usually gets absorbed well by the oral administration ; however, nearly 1/3rd of an oral dose is metabolized by both **intestinal organisms** and **antibiotics** that ultimately affect the quantam absorbed. Furthermore, in doses greater than 80 mg/m^2 the amount absorbed is further reduced to the extent of 30-50%. It has been duly observed that almost 50% of the '**drug**' is bound to plasma-protein, however, it fails to gain an access to the cerebrospinal fluid (CSF) due to the glaring fact that it gets ionized overwhelmingly and outwardly transported at the *choroid plexus*. As a result it should be administered intrathecally for its judicious application in CNS.

The plasma clearance of the '**drug**' is found to be triexponential having a distribution half-life of nearly 45 minutes ; whereas, a *second-phase* of approximately extending upto 3.5 hours.* It has an elimination half-life of 6 to 69 hours. The renal tubular secretion is responsible for nearly 80% of the elimination.

*Perhaps due to an enterohepatic component—as about 10% of the '*drug*' is secreted into the **bile**.

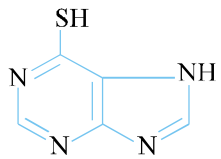
Note. The simultaneous administration of drugs like : probenecid, salicylate and other NSAIDs etc., directly interfere with its secretion ; and hence, should be avoided as far as possible.

2.2.2. Analogues of Purines

Purines are integral components of RNA, DNA and coenzyme that are synthesized in proliferaton of cancer cells. Therefore, an agent that antagonizes the purine will certainly lead to formation of false DNA and these include analogues of natural purine bases, nucleosides and nucleotides.

A few drugs belonging to this classification are, namely : Mercaptopurine and Azathiopurine :

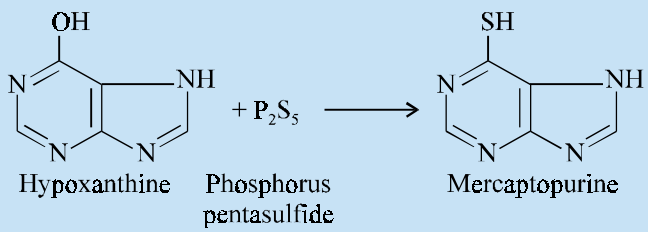
A. *Mercaptopurinum* BAN ; *Mercaptopurine* USAN ;



o-Mercapto-6-purine ; 6 MP ; BP(1973) ; USP ;

Purinethol(R) (Burroughs Wellcome) ;

Synthesis

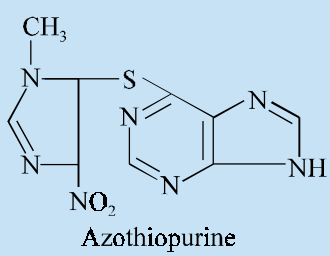


It may be prepared by the interaction of hypoxanthine with phosphorus pentasulphide.

Mercaptopurine is found to inhibit experimental orthoimmune encephalomyletis and thyroiditis and hence used in combination with vincristine, methortrexate and prednisone in the treatment of childhood leukemia. As such 6-MP may cause hyperuricamia but it is usually administered with *allopurinol*—an analogue of hypoxanthine which blocks the conversion of 6-MP to uric acid and hence the dose of 6-MP is reduced and still the desired response is obtained.

Dose. *Oral, usual, initial for children and adults : 2.5 mg per kg body weight daily, but the dosage varies as per individual response and tolerance.*

***B. Azathiopurine* BAN, USAN,**

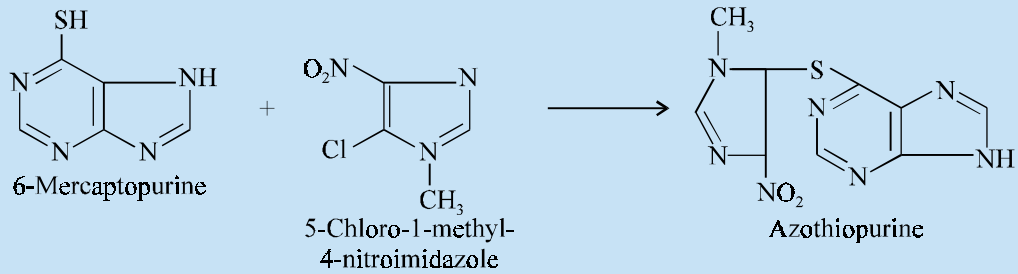


Azothiopurine

6-[1-Methyl-4-nitromidazole-5 yl] thio] purine ;BP ; USP ;

Imuran(R) (Burroughs Wellcome) ;

Synthesis



It is prepared by treating 6-mercaptopurine with 5-chloro-1-methyl-4-nitroimidazole.

The main use of **azathiopurine** is as an adjunct for the management and prevention towards the rejection of renal homotransplants.

Dose. *Usual, adult, and children : 1 to 25 mg per kg body weight daily by mouth.*

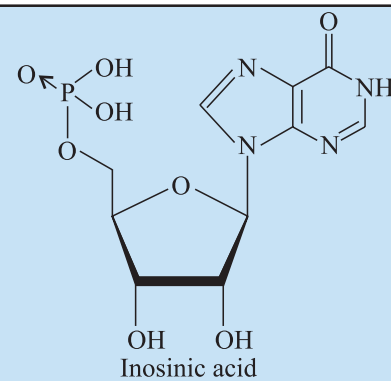
2.2.2.1. Mechanism of Action

The **mechanism of action** of the two medicinal compounds described under Section 2.2.2 shall be dealt with in the sections that follows :

2.2.2.1.1. Mercaptopurine

The '**drug**' gets converted to 6-thioinosinic acid that predominantly serves as an antimetabolite to inhibit synthesis of **adenine** and **guanine** ; besides, it also presents conversion of *purine bases* into the corresponding **nucleotides**.

It also mimics **inosinic acid** thereby causing a negative feedback suppression of the synthesis of **inosinic acid**. It has been observed that a portion of the '**drug**' gets converted to **thioguanine**, which is ultimately incorporated into both DNA and RNA to give rise to the formation of defective nucleic acids. In this manner the synthesis and functionalities of the resulting nucleic acid are impaired in various ways. It finally helps in the *inhibition of cell mitosis.*



Inosinic acid

It has been found that the systemic bioavailability of mercaptopurine *via* the oral route varies from 5-37%, due to its first-pass metabolism in the intestinal mucosa and liver, wherein the two biochemical reactions usually take place, namely : (*a*) **oxidation by xanthine oxidase** ; and (*b*) **S-**

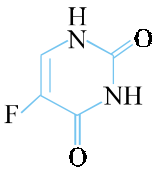
methylation. The '**drug**' gets bound to plasma protein to nearly 20%. Its volume of distribution (v_d^{ss}) is much higher in comparison to the extracellular space ; however, the access to CSF is minimal. The half-life in children is 21 minutes and in adults 47 minutes.

2.2.3. Analogues of Pyrimidines

Pyrimidine analogues have the capacity to interfere with the synthesis of pyrimidine nucleoside and hence the DNA synthesis. Aside from their **antineoplastic** effects they are also found to be equally effective in psoriasis and fungal infections.

A few characteristic compounds of this category are, namely : **Fluorouracil** and **Cytarabine**.

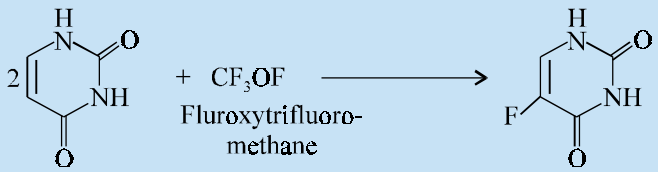
A. Fluorouracil BAN, USAN,



5-Fluoro-2, 4 (1H, 3H)-pyrimidinedione ; 2, 4-Dioxo-5-fluoropyrimidine ; USP ;

Efudex(R) (Roche) ; Fluoroplex(R) (Allergan) ;

Synthesis

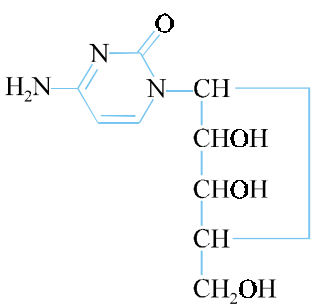


This official compound is prepared by the direct fluorination of **uracil** with **fluoroxytrifluoromethane**.

It is used in the palliative treatment of carcinoma of the breast, pancreas, prostrate, colon and hepatoma for which surgery or irradiation is not possible. It is also found to be beneficial in tropical treatment of premalignant solar keratosis.

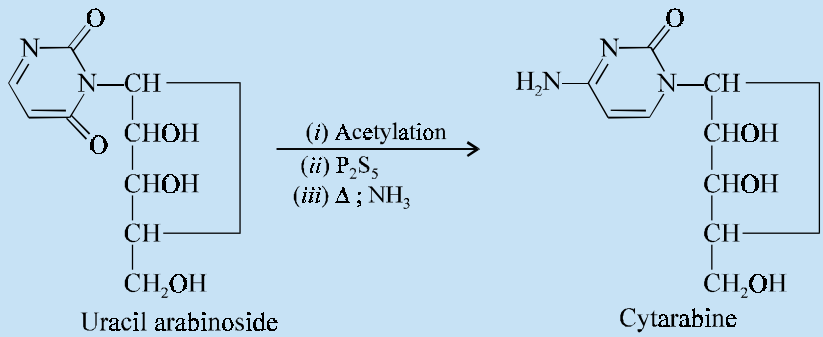
Dose. *Usual, iv injection : 1.2 mg per kg body weight daily to a maximum of 1 g daily for 3 or 4 days.*

B. *Cytarabine* BAN, USAN,



o-Amino-4-arabinofurannosyl-1-oxo-2dihydro-1, 2-pyrimidine ; Cytosine arabinoside ; USP ; Aracytin$^{(R)}$ (Upjohn) ; Cytosar-U$^{(R)}$ (Upjohn).

Synthesis



Cytarabine may be synthesized by the acetylation of uracil arabinoside followed by treatment with phosphorus pentasulphide and subsequent heating with ammonia.

It is indicated in both adult and childhood leukemia. It is specifically useful in acute granulocytic leukemia and found to be more effective when combined with **thioguanine** and **daunorubacine**.

Dose. *Usual adult, and children for leukemia : 2 mg per kg body weight intravenously per day for 0 days.*

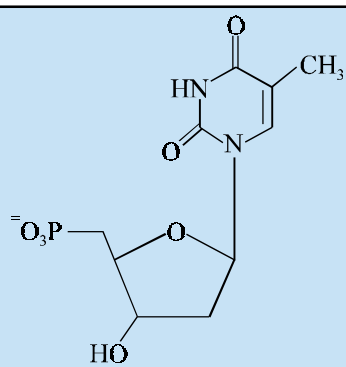
2.2.3.1. Mechanism of Action

The **mechanism of action** of **fluorouracil** and **cytarabine** discussed under Section 2.2.3 shall now be treated individually as under :

2.2.3.1.1. Fluorouracil

The '**drug**' is a congener of uracil which eventually serves both as a surrogate and as an antimetabolite of the nueleotide. Interestingly, its metabolite, **5-fluorodeoxyuridine-5′-monoplosphate (FUMP)**, blocks the synthesis of **thymidylic** and hence of **deoxyribonucleic acid (DNA**).

It also gets incorporated into the RNA directly. The '**drug**' is poorly absorbed orally and hence shows variable first-pass metabolism of the drug but the gut and the liver ; and hence, IV administration is an absolute necessity. It has been observed that nearly 60% of it gets metabolized to CO_2 ; however, more than 15% is excreted through the urine. The '**drug**' gains entry into the CSF and effusions. The plasma half-life is nearly 10 minutes ; however, the **active metabolite FUMP,** may be detectable for quite a few days at a stretch.



2.2.3.1.2. Cytarabine

The '**drug**' is a **pyrimidine nucleoside antimetabolite** which is cytotoxic to a plethora of cell-types. Precisely the induction of the enzyme **nucleotidase** into DNA inhibits polymerization *via* termination of strand synthesis. It is **S-phase specific**.

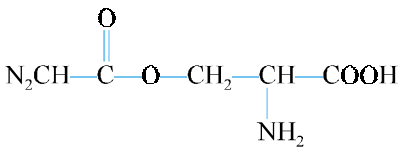
As the '**drug**' is not absorbed quite effectively by oral administration, hence its oral bioavailability is merely 0.2. Nevertheless, it penetrates right into the CSF and accomplishes a concentration upto 40% in plasma. It gets destroyed *in vivo* to an extent of 90% by **deamination**. Its plasma half-life ranges between 1-3 hours. The elimination half-life in the CSF stands at 3.5 hours. The '**drug**' undergoes **detoxification** through the entire body ; and, therefore, perhaps it may be administered even in patients with renal impairment, however, the dosage could be lowered accordingly.

2.2.4. Amino Acid Antagonists

The **amino acid antagonists** broadly act as a **glutamine antagonists** in the synthesis of formylglycinamidine ribotide from glutamine and formylglycinamide ribotide.

Example. Azaserine ;

A. Azaserine USAN,



o-Diazoacetyl-L-serine ;

CI-337$^{(R)}$ (Parke Davis) ;

Azaserine inhibits the growth of sarcoma 180 and several leukemias. In clinical trials, although there was improvement in some cases of Hodgkin's disease, acute leukemia in children and chronic lymphocytic leukemia, the results in general were not very encouraging.

2.2.4.1. Mechanism of Action

The mechanism of action of **azaserine** is discussed as under :

2.2.4.1.1. Azaserine

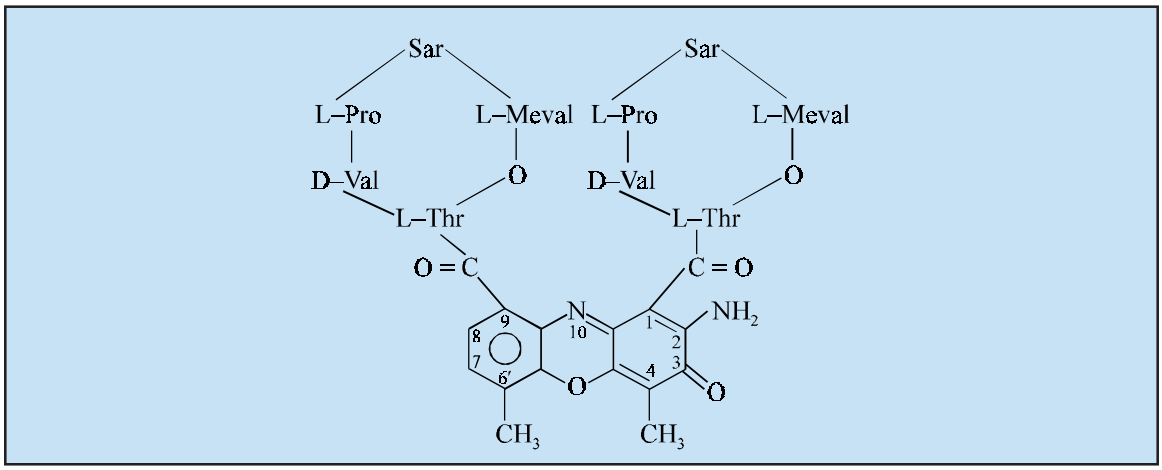
The '**drug**' is believed to be a glutamine antagonist that specifically inhiits **purine biosynthesis** and thus may exert antitumour activity.

2.3. Antibiotics

The recognitiion of **antibiotics** as an important class of **antineoplastic agents** is quite recent. Consequently, the production of **antineoplastic agents** through proper strain selection and controlled microbial fermentation conditions may ultimately optimize the formation of a particular component in an antibiotic mixture.

A few important members of this category are described below, namely ; **Dactinomycine** ; **Daunorubicin** ;

A. *Dactinomycine* USAN,



Actinomycin D ; USP ;

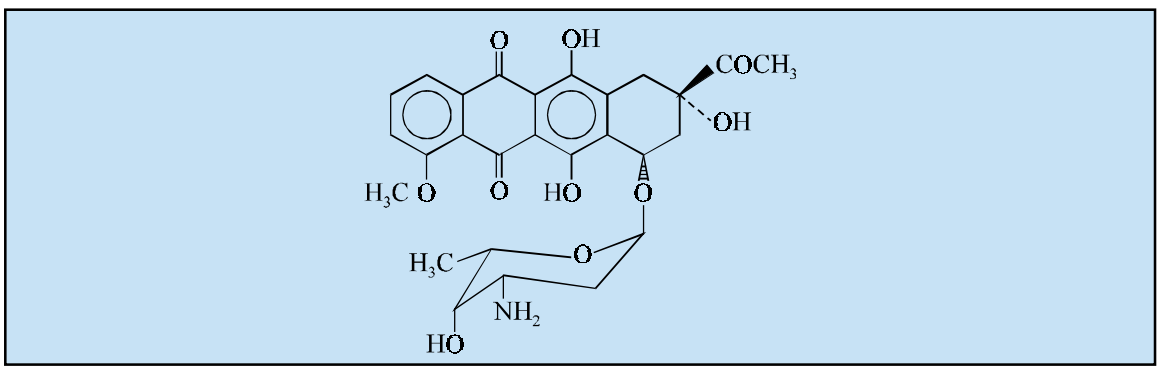
Cosmegen(R) (Merck, Sharp & Dohme).

The first **antibiotic** to be isolated from a species of *Streptomyces* was Actinomycin A and many related antibiotics including **Actinomycin D** were latter obtained. **Actinomycin C** was the first to be tried on neoplastic diseases. **Actinomycin D** is commercially available as **Dactinomycine**. It is found to the acitve against **L-1210, P-1534, P-388 and adenocarcinoma strains**. It binds to DNA thereby preventing DNA transcription.

It is used in the treatment or rhabdomyosarcoma in children and methotrexate-resistant choricarcinoma in women. It has also been used to inhibit immunoligical response particularly the rejection of renal transplants.

Dose. *Adults, iv, 0.01 mg (10 mcg) per kg body weight ; Children : 0.015 mg (15 mcg) per kg body weight for not more than 5 days.*

B. *Daunorubicin* BAN ; *Daunorubicin Hydrochloride* USAN



5,12-Naphthacenedione, (8S-*cis*)-8-acetyl-10-[(3-amino-2,3,6-trideoxy)-α-1-lyxo-hexanopyranosyl) oxy]-7, 8, 9, 10-tetrahydro-6, 8, 11-trihydroxy-10-methoxy, hydrochloride ;

Ondena(R) (Bayer).

Anthracyclines constitute another complex and bigger family of antibiotics. They mostly occur as **glycosides of the anthracyclinones** (aglycone residue). They act by intercalation with the DNA in both normal and neoplastic cells.

Daunorubicin is useful in the treatment of acute lymphoblastic leukemia in children. It is normally employed in combination therapy, for instance : with cytosine arabinoside in the treatment of myclogenous leukemia ; with **cytarabine** in the treatment of non-lymphoblastic leukemia in adult.

Dose. For acute mycloblastic leukemia : 45 to 60 mg per m^2 body-surface daily for 3 days by injecting a solution in sodium chloride injection into a fast-running infusion of sodium chloride.

2.3.1. Mechanism of Action

The **mechanism of action** of **dactiromycin** and **daunorubicin** will be dealt with individually as under :

2.3.1.1. Dactinomycin

The '**drug**' specifically inhibits the **DNA-dependent RNA-polymerase.** Interestingly, the drug also significantly potentiates **radiation recall** (otherwise known as '**radiotherapy**'). It also serves as a *secondary (efferent) immunosuppressive agent.* It has been demonstrated that almost 50% of the dose is excreted in fact into the bile and 10% into the urine ; the half-life is nearly 36 hour. The drug does not pass the **blood-brain barrier (BBB)**.

2.3.2. Daunorubicin Hydrochloride

The '**drug**' intercalates into DNA, inhibits **topoisomerase** II, yields oxygen radicals, and ultimately inhibits DNA synthesis. It can invariably prevent and check cell division in doses that virtually fail to interfere directly with the nucleic acid synthesis.

It has been observed that the oral absorption is reasonably poor ; and, therefore, it must be administered IV. The half-life of distribution is about 45 minutes and of elimination, nearly 19 hours. The active metabolite, **daunorubicinol**, has a half-life of almost 27 hours. The '**drug**' gets metabolized largely in the liver, and also secreted right into the bile (ca 40%).

CAUTION : **Dosage should be lowered in instances where liver or renal insufficiencies occur.**

2.4. Plant Products

Plant products have been used extensively in the treatment of malignant disease since thousands of years, but the studies of Dustin in 1938 on the cytotoxicity of colchicin heralded the start of the search for **natural antineoplastic drugs**. Today a large number of chemical constituents isolated from naturally occurring plant products have proved to the quite efficacious as **antitumour agents**.

An attempt is made here to review the action, clinical usefulness, their sources and the classification is done based on their chemical nucleus ; *viz.*,

(*a*) Imides and Amides

(*b*) Tertiary Amines

(*c*) Heterocyclic Amines

(*d*) Lactones

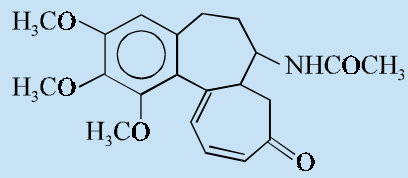
(*e*) Glycosides

2.4.1. Imides and Amides

Examples. Colchicine ; **Narciclasine** ;

A. Colchicine

Colchicine occurs as the major alkaloid of the autumn crocus, *Colchicum autumnale* and the African climbing Lily, *Gloriosa superba* Linn., (Family : *Liliaceae*).



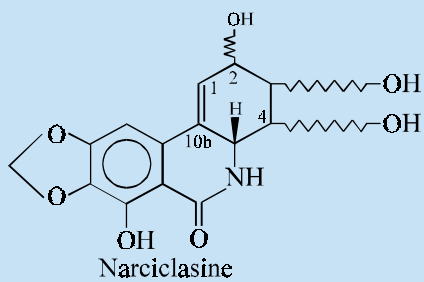
Colchicine

It arrests mitosis at the metaphase preventing anaphase and telophase. It was observed that colchicine diminishes deoxy-cytidylate aminohydrolase activity in Ehrlich ascites cells suggesting thereby that its action on mitosis and DNA synthesis could be by this method only. It is mainly used in terminating acute attacks of gout.

However, its derivative, **demecoloine** (**Colcemid**) is found to be active against myelocytic leukemia.

B. ***Narciclasine***

Narciclasine, an alkaloid isolated from the bulbs of **narcissus**, possesses antimitotic activity against S-180 in ascites form suggesting thereby that it acts essentially as a metaphasic or preprophasic poison.



Narciclasine

Both chemical and spectral studies suggest the above structure of narciclasine, but unlike other members of the **amaryllidaceae group of alkaloids** it possesses no basic properties.

2.4.1.1. Mechanism of Action

The **mechanism of action** of **colchicine** and **narciclasine** described under Section 2.4.1 will be treated as under :

2.4.1.1.1. Colchicine

The precise mechanism of action of this '**drug**' is not yet known, although it is believed to minimize appreciably leukocyte motility, phagocytosis, and also **lactic acid production**, thereby lowering the deposition of **urate crystals** and the **inflammatory response.** In fact, all these effects combinedly relate to the **interference of colchicine** upon the cellular mitotic spindles progressively.

It is found to be absorbed very well after oral administration ; and almost 31% gets bound to plasma protein. It is usually eliminated by the faecal and urinary routes.

CAUTION. ***The 'drug'*** **must be given with great caution particularly to debilitated and aged patients ; and also for those who have a history of cardiac, renal, hepatic, GI, or hematological problems.**

2.4.1.1.2. Narciclasine

The '*drug*' exert its action due to its inherent antimitotic agent. It also inhibits protein synthesis. It is regarded to be the most active antitumour agent of the *Amaryllidaceae* alkaloids.

2.4.2. Tertiary Amines

It includes a good number of dimeric, acyclic and phenanthro compounds and a few of them are discussed below :

(*i*) Dimeric indole alkaloids : *e.g.,* Vinblastine ; Vincristine ;

(*ii*) Dimeric tetrahydroisoquinolines : *e.g.,* Thalicapine ; Thalidasine ;

(*iii*) Acyclic tertiary amines : *e.g.,* Solapalmitine ; Solapalmitenine ;

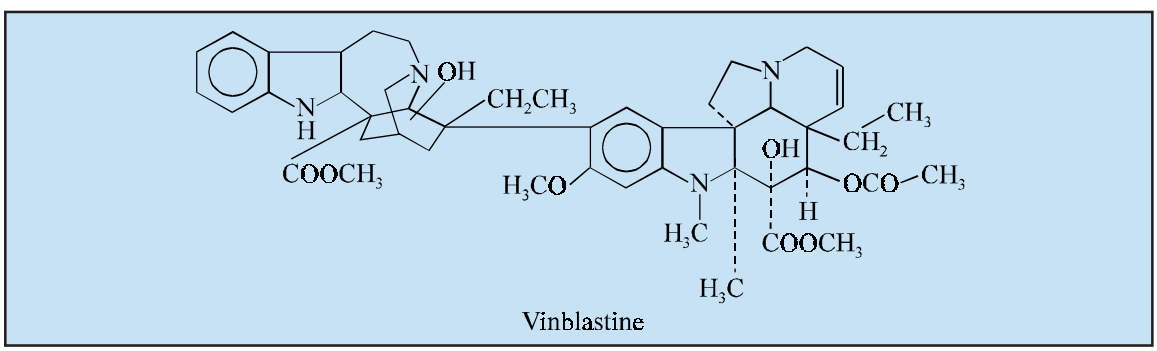
(*vi*) Phenanthroquinilizidines : *e.g.,* Cryptoleurine ;

(*v*) Phenanthroindolizidines : *e.g.,* Tylophorine ; Tylocrebrine ; Tylophorinine ; Phenanthroindolizidine ;

2.4.2.1. *Dimeric Indole Alkaloids*

So far about 72 alkaloids have been isolated from *Vinca rosea* Linn, genus *Catharanthus roseus* (**Family** : *Apocynaceae*). Out of these 24 dimeric alkaloids only six possess **antineoplastic activity** but specifically two *i.e.*, **vincristine**, **vinblastine**, are used clinically in human neoplasms. These are cell-cycle specific agents.

A. *Vinblastine* BAN



Vinblastine

Vincaleucoblastine ; Vinblastine Sulfate USP ; Vinblastine Sulphate BP ;

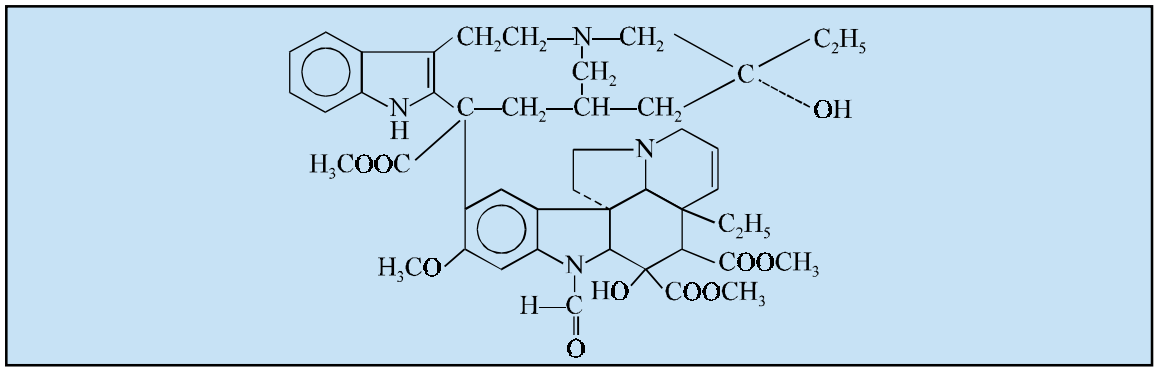
Velban$^{(R)}$ (Lilly) ;

The alkaloid **vinblastine** is made up of two moieties namely : **catharanthine** and **vindoline** which is found to occur in the plant.

It is used in the treatment of Hodgkin's disease, monocytic a drug of third choice in the treatment of neuroblastoma, breast tumours and mycosis fungoides. It is combined with vincristine in the treatment of lymphocytic and myeloblastic leukemia in children.

Dose. *Intravenously as a solution containing 1 mg per ml in sodium chloride injection.*

B. *Vincristine* BAN ; *Vincristine Sulfate* USAN :



Vincristine Sulfate USP : Vincristine Sulphate BP ;

Oncovin(R) (Lilly) ; Vincasar PFS(R) ;

It is employed for the treatment of acute leukemia in children, neuroblastoma, Wilm's tumour and rhabdomyosarcoma. It is found to induce remission in lymphosarcoma and Hodgkin's disease. It is also used in combination therapy with **daunomycin** and **prednisone** in dramatic remission of leukemia.

Dose. *Intravenously as a solution containing 0.01 to 1 mg per ml in sodium chloride injection.*

2.4.2.1.1. Mechanism of Action

The **mechanism of action of vinblastine** and **vincristine sulfate** shall be treated as under :

2.4.2.1.1.1. Vinblastine

The '**drug**' specifically interferes with the assembly of the microtubules, by effectively combining with tubulin, thereby causing a mitotic arrest in the metaphase. Besides, there exists enough supportive evidence that vinblastine exerts its antitumour effect significantly with glutamate and aspartate metabolism. It is, however, pertinent to mention here that the extent of antineoplastic spectrum and the degree of toxicity are distinctly different in comparison to vincristine, that incidently also interacts with tubulin. It has been found that in plasma the '**drug**' is almost 75% protein bound. It usually manifests a **three-compartment kinetics,** of which the second-phase essentially exhibit a half-life ranging between 1–1.5 hours, and an elimination half-life varying between 18-40 hours. Vinblastine is metabolized extensively by the liver ; and, therefore, the dosage regimen has got to be reduced by almost 50% in such patients who have confirmed impaired liver function.

2.4.2.1.1.2. Vincristine Sulfate

The '**drug**' progressively gets combined to the protein tubulin, and subsequently provides a check upon the assembly of microtubules, thereby causing a complete disruption of various cellular processes, including essentially mitosis and spindle formation. Besides, vincristine appreciably suppresses the strategic syntheses of proteins and RNA.

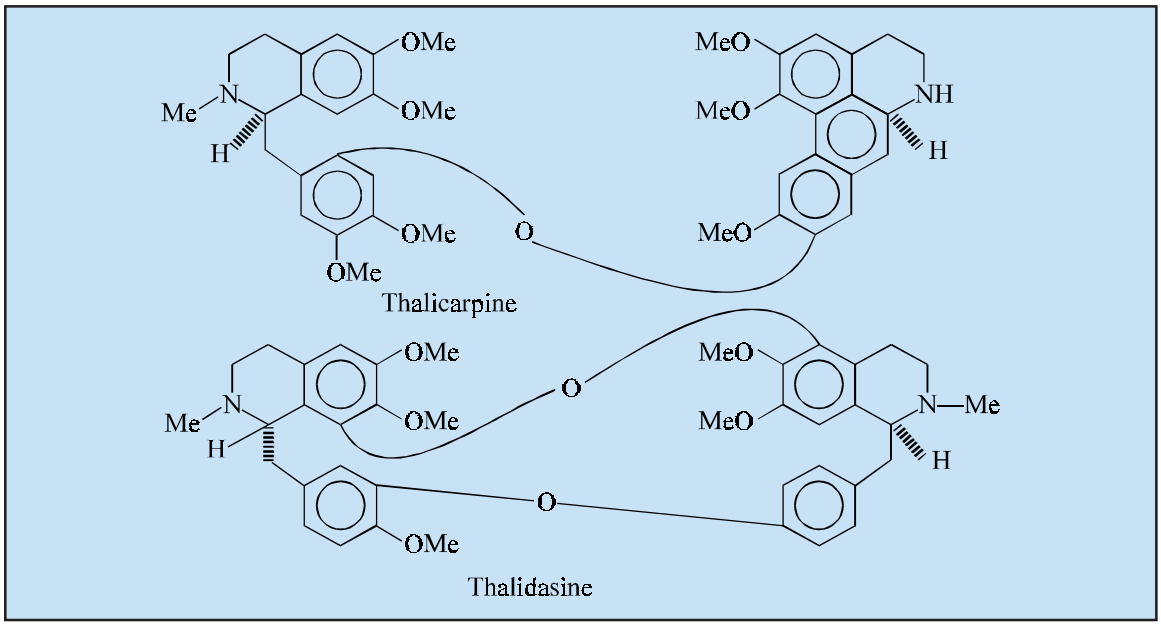
It manifests a three-compartment kinetics, having the half-lives of 0.08, 2.3 and 8.5 hour respectively.It is usually secreted directly into the bile upto 70%. Nearly 12% gets excreted in urine. As the '*drug*' cannot penetrate into the brain ; therefore, it has a little usage for the CNS leukemias.

2.4.2.2. *Dimeric Tetrahydroisoquinolines*

In fact only two alkaloids have been isolated from the roots of *Thalictrum dasycarpum* (Family : *Ranunculaceae*) by systematic fractionation namely : **thalicarpine** and **thalidasine**.

A. *Thalicarpine*

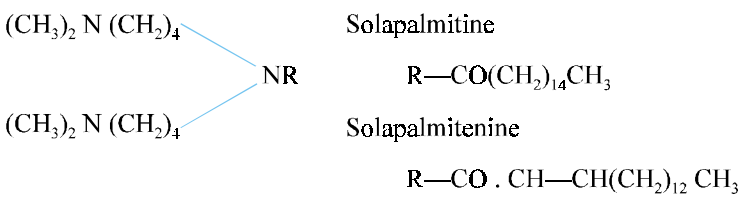
It has also been isolated from *Thalictrum minus* Linn., *Thalictrum revoluctum* and *Hernandia ovigera* (**Family** : *Hernandiaceae*).



Both these compounds have shown activity in mice, dog and rats against Walker 256 carcinomas.

2.4.2.3. *Acyclic Tertiaryamines*

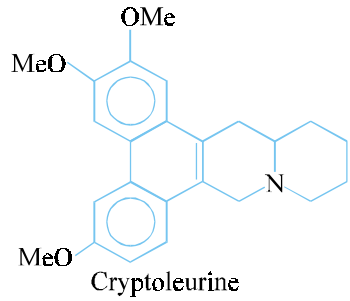
The Bolivian plant *Solanum tripartitum* (**Family** : *Solanaceae*) gave two alkaloids, namely : **solapalmitine** and **solapalmitenine**.



Both these alkaloids have shown *in vivo* activity against Walker 256 and their therapeutic indices do not call for further clincial studies.

2.4.2.4. Phenanthroquinolizidines

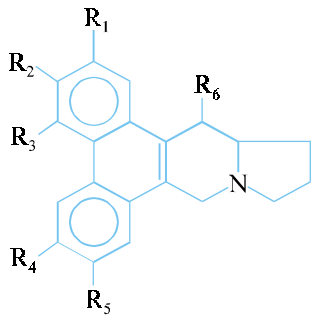
Cryptoleurine has been isolated from *Bochmeria cylindrica* (Family : *Urticaceae*) and it is found to possess highly specific cytotoxic action against **Eagle's KB carcinoma** but inactive against many experimental tumours. A number of its analogues have been synthesized for antineoplastic studies.



Cryptoleurine

2.4.2.5. *Phenanthroindolizidines*

Four alkaloids have been isolated from *Tylophora crebriflora* (**Family** : *Asclepiadaceae*) by **systematic** fractionation, namely : **Tylophorine** ; **Tylocrebrine**, **Tylophorinine**, and **Phenanthroindolizidine**.



Tylophorine : $R_1 = R_2 = R_4 = R_5 = OCH_3$ & $R_3 = R_6 = H$;

Tylocrebrine : $R_1 = R_6 = H$ & $R_2 = R_3 = R_4 = R_5 = OCH_3$;

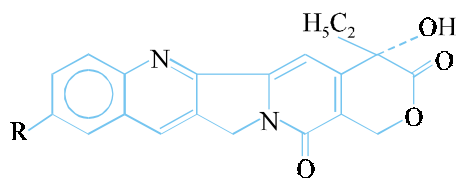
Tylophorinine : $R_1 = R_3 = H$; $R_6 = OH$ & $R_2 = R_4 = R_5 = OCH_3$;

Phenanthroindolizidine : $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$;

Tylophorine is active against C-755 and W-256 and tylocrebrine against C-755, P-388, lymphocytic leukemia and L-1210.

2.4.3. Heterocyclic Amines

These alkaloids namely : **camptothecin**, **hydroxycamptothecin** and **methoxy camptothecin** were isolated from the Chinese tree *Camptotheca acuminata* (**Family** : *Nyssaceae*).



Camptothecin : R = H ;

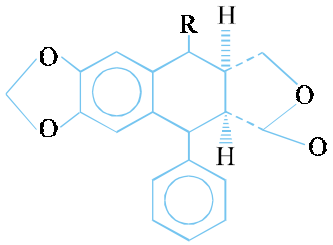
Hydroxycamptothecin : R = OH ;

Methoxycamtothecin : $R = OCH_3$;

Both **camptothecin** and **hydroxycamptothecin** are found to be active against rodent leukemia and solid tumours.

2.4.4. Lactones

Podophyllotoxin and **deoxypodophyllotoxin** are the two alkaloids obtained from the Himalayan shrub *Podophyllam emodi* and the May Apple *Podophyllum peltatum* (**Family** : *Berberidaceae*).



Podophyllotoxin : R = OH ;

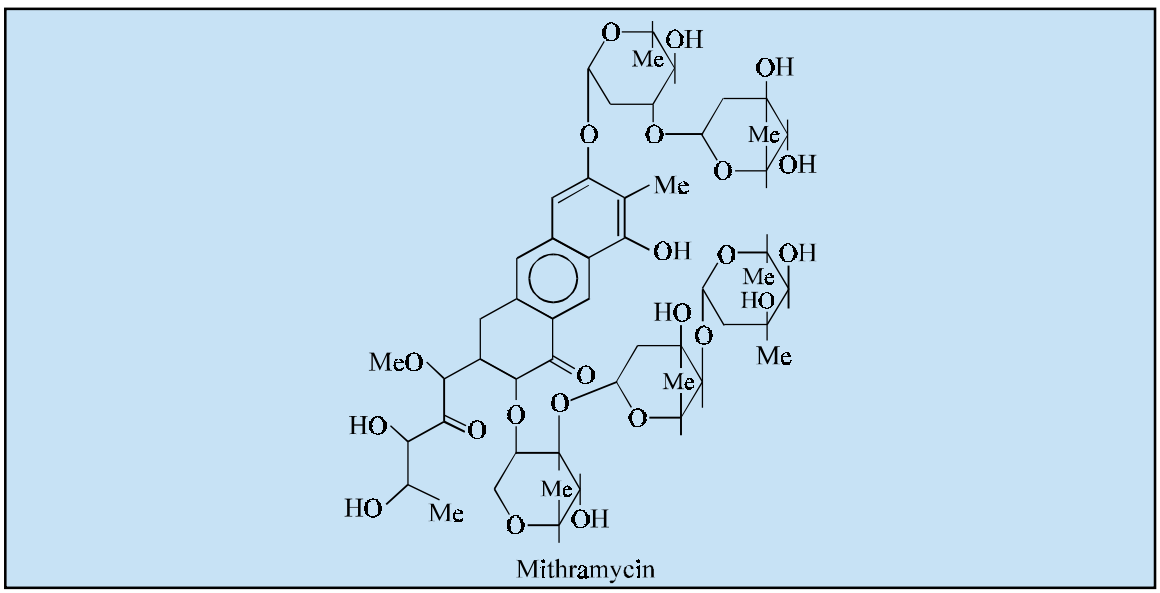
Deoxypodophyllotoxin : R = *o*-glucosyl ;

Podophyllotoxin is an aromatic lactone that arrests the **metaphase activity in the DNA synthesis**.

2.4.5. Glycosides

Two glycosides that possess antineoplastic properties are discussed here, namely : **Mithramycin** (**Aureolic Acid**) and **β-Solamarine**.

A. *Mithramycin* BAN, USAN,



Plicamycin ; Aureolic Acid ; USP ;

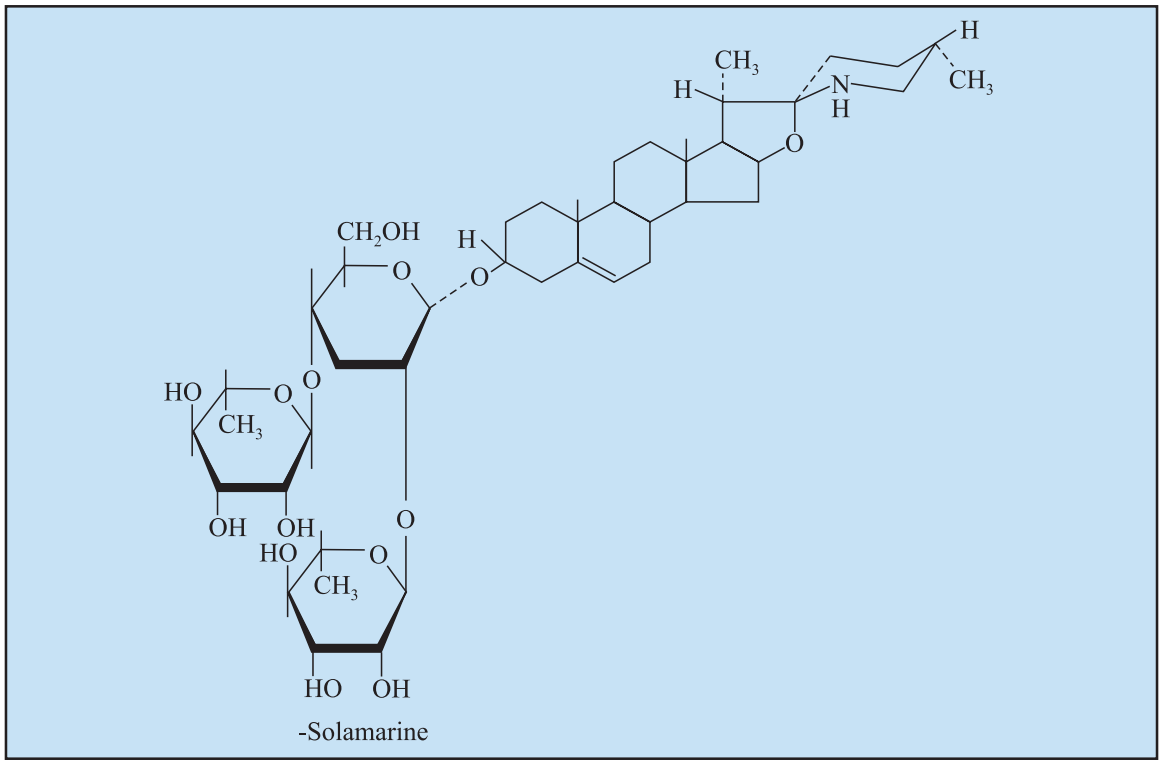
Mithracin$^{(R)}$ (Pfizer-Roarig ; Dome) ;

It is isolated from *Streptomyces argillaceus.* It is employed in the treatment of breast cancer, malignant lymphomas and carcinoma of the stomach.

Dose. *For hypercalcamia and hypercalcuria : usual 25 mcg per kg daily by slow iv infusion for 3 or 4 days.*

The steroidal alkaloidal glycoside **β-solamarine** is isolated from woody night-shade *Solanum dulcomara* Linn., (**Family** : *Solanaceae*).

It is found to be active against S-180, strain.



-Solamarine

2.4.5.1. Mechanism of Action

The mechanism of action of medicinal compound discussed under Section 2.4.5 shall be treated separately in the sections that follows :

2.4.5.1.1. Mithramycin (Plicamycin)

The '*drug*' exerts its action by getting itself bound to **guanine-rich DNA** and thereby helps in inhibiting **DNA-dependent RNA polymerase**. It predominantly acts during the S-phase. As it is found to suppress *osteoclast activity**, it is invariably employed to treat *malignant hypercalcemia*** that is both unresponsive to *conventional treatment* and other severe, *refractory hypercalcemias*.

2.5. Miscellaneous Compounds

There are various compounds that exert **neoplastic activity** both belonging to synthetic and natural origins. A few such compounds are described below :

Examples : Cisplatin, **Imidazole Triazines**, **Hycanthone**, **Pipobroman**,

***A. Cisplatin* BAN, USAN,**

cis—[Pt $(NH_3)_2$ Cl_2]

Cisplatine ; *cis*-Dichlorodiamine platinum ;

Platinex(R) (Bristol-Meyers) ; Neoplatin(R) (Mead-Johnson) ;

---

* A device for fracturing bones for therapeutic purposes.

**Neoplasms which essentially cause dissolution of bone salts.

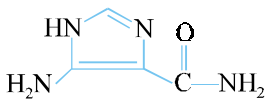
The effectiveness of transition-metal complexes, particularly platinum complexes, as experimental **antineoplastic agents** has been reported in recent years. **Cisplatin** is the prototype platinum complex having **antineoplastic activity**.

It is employed in combination with **vinblastine** and **bleomycin** for the treatment of metastatic testicular tumours. It is also used for the remission of metastaticovarian tumours when given either alone or in combination with **doxorubicin**. It also exhibits activity against a host of other tumours, such as : cervical cancer, neck and head cancer, penile cancer, bladder cancer and small-cell cancer of the lung.

Dose. *Usual, for metastatic testicular tumours 20 mg/m^2 iv daily for five days, followed every 3 weeks for 3 courses : for metastatic ovarian tumours 50 mg/m^2 iv once every 3 weeks.*

B. *Imidazole Triazines :*

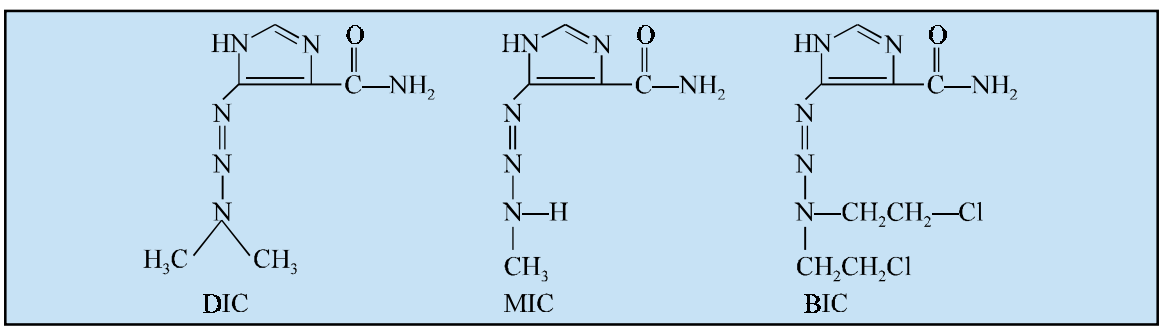
Windans and Langenbeck (1923) first described the synthesis of 5-aminoimidazole-4-carboxamide (AIC) which they later on used for the synthesis of purines :



AIC

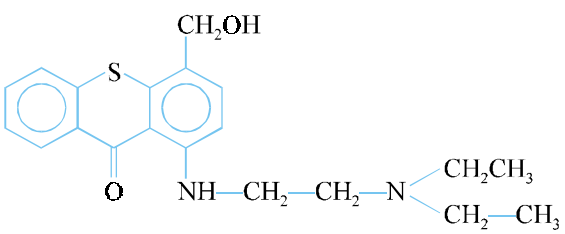
Its structural modification resulted into the synthesis of the following *three* compounds, namely :

5-(3, 3-dimethyl-1-triazeno) imidazole-4-carboxamide **(DIC)** ; 5-3, 3-bis (2-chloroethyl)-1-triazeno) imidazole-4-carboxamide **(BIC)** ; 5-(3-monomethyl-1-triazeno) imidazole-4-carboxamide **(MIC)** ;



DIC (NSC 45388) is found to be active against mouse leukemia L 1210, sarcoma 180 and adenocarcinoma. BIC was found to be most potent suggesting thereby that halo-substitution are often more potent in antineoplastic activity. At present **DIC** is mostly employed in malignant malanoma. It is used in combination with **adriamycin**, **bleomycin** and **vinblastine** in the treatment of Hodgkin's diseases and in sarcomas with **adriamycin**.

***C. Hycanthone* USAN**

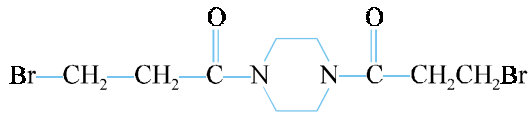


[(Diethlamino-2-ethyl) amino]-1-hydroxymethyl-4-thioxanthenone-9 ;

Etrenol(R) (Winthrop) ;

Hycanthone, which was earlier identified as an antischistosomal drug, found to possess antineoplastic activity in animals. It is comparatively non-toxic. Besides, it is an intercalating agent which inhibits both DNA and RNA synthesis.

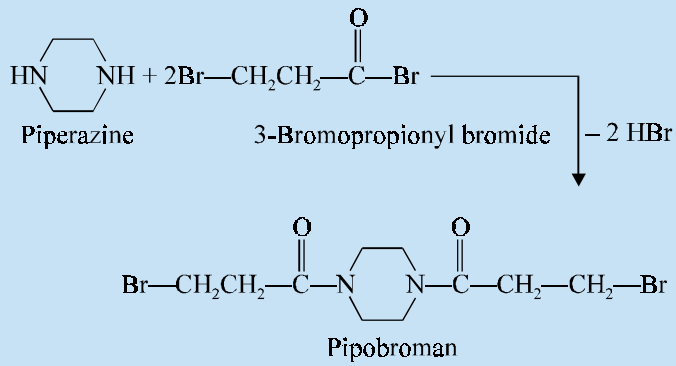
D. *Pipobroman* USAN,



Bis-(bromo-3-propionyl)-1, 4-piperazine ; USP,

Vercyte(R) (Abbott) ;

Synthesis



It is prepared by the interaction of piperazine with two moles of 3-bromopropionyl bromide.

It is used in patients with chronic granulocytic leukemia refractory to busulfan. It is also employed for the treatment of polycythemia vera.

Dose. *Usual, initial : 1 to 1.5 mg per kg body weight daily.*

E. *Asparaginase* USAN *; Colaspase* BAN ;

L-Asparaginase amidohydrolase :

Leunase(R) (May & Baker) : Elspar(R) (Merck, Sharp & Dohme) ; Crasnitin(R) (Bayer) ;

It is a preparation from *Escherichia coli* containing the enzyme L-asparaginase amidohydrolase.

It is used in patients suffering from acute lymphocytic and other leukemias.

Dose. *Intravenously : 1000 units per kg body weight daily for 10 days following treatment with vincristine or prednisone.*

2.5.1. Mechanism of Action

The **mechanism of action** of certain medicinal compounds discussed under Section 2.5 shall now be dealt with individually as under :

2.5.1.1. Cisplatin

The '**drug**' essentially cross-links DNA ; and, therefore, behaves like alkylating antineoplastic agents. In general, the platinum complex acts as a potent inhibitor of DNA polymerase. Based on adequate

supportive evidences it has been duly established that there exists a bondage between DNA and platinum complex, wherein the two Cl^- ions are duly displaced by N or O atoms of purines. This evidence is fully substantiated by concrete experimental findings, such as : (*a*) **enhanced sedimentation coefficient** ; (*b*) **hyperchromicity shown by the DNA-UV-spectrum** ; and (*c*) **selective and specific reaction occurring between the Pt-complex and guanine over other bases**.*

Cisplatin is *not* well absorbed by oral administration, and hence, must be given IV. The '*drug*' gets bound to plasma proteins to the extent of 90%. It fails to cross the blood-brain barrier (BBB). It gets secreted chiefly *via* renal route, partly by tubular secretion ; however, the overall pattern is found to be '**nonlinear**' in nature. It has been observed that the prevailing distribution half-life of the unbound drug is 25-49 minutes and the elimination half-life of total Pt ranges between 58-73 hours, which may get extended upto 240 hours in *anuria*.**

Note. Sodium thiosulphate decomposes cisplatin and complxes with Pt, and in this manner affords protection against renal damage and certain other toxicity.

2.5.1.2. Pipobroman

The '**drug**' exerts its action due to its alkylating properties. Importantly, it is invariably held in reserve for usage in such patients who have virtually turned refractory to **X-irradiation** and **busulfan** in the severe case of **leukemia** and **phlebotomy**.***

CAUTION : It should not be used in pregnancy.

2.5.1.3. Asparaginase

It has been observed that the ensuing protein synthesis in a good number of normal and malignant cell types depends partially on **exogenous asparagine** ; and in a few cells like-*leukemic cells* and *lymphoblasts* is dependent almost completely. Consequently, the enzymatic destruction of asparagine by the enzyme asparaginase duly injected into plasma usually deprives the dependent cells of the essential asparagine thereby causing predominantly *three* vital effects, namely : (*i*) **partial cell-death** ; (*ii*) **arrest cell growth** *;* and (*iii*) **tumour regression**.

Asparaginase (the **enzyme**) is found to protect certain tissues and malignant tumours from some known **antimetabolites**, such as : **methotrexate**, **ara-C**, presumably by directly preventing DNA synthesis.

Ervinia (Porton) *asparaginase* is observed to be less sensitizing in comparison to that obtained from *E. coli*. Besides, Ervinia asparaginase is designated as an '**orphan drug**' which is virtually reserved for usage particularly in patients who are found to be allergic to **asparaginase** obtained from *E. coli.* Interestingly, both enzymes do exhibit **immunosuppressant activity.**

The '**drug**' exhibits extremely poor extravascular tissue penetration ; and, therefore, gets cleared from plasma in a quite sluggish and unpredictable manner. Nevertheless, the elimination is *biphasic*, having an inital half-life of 4-9 hours and a terminal half-life ranging betwen 1.4 to 1.8 day.****

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* Sartorelli AC and Johns DJ (eds) : **Handbook of Experimental Pharmaeology**, Vol. 38, Pt. 2, Springer = Verlag, New York, pp. 829-838, 1975.

**Absence of urine formation.

*** The surgical opening of a vein to withdraw blood.

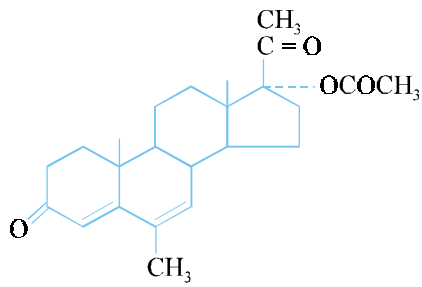
****Physicians' Desk Reference**, Medical Economics, Oradell N.J., 33**rd** edn., (p. 749) 1979.

2.6. Hormones

Hormones has the ability to suppress mitosis in lymphocytes and this effect is duly utilized in the treatment of neoplastic diseases. **Adrenocorticosteroids** specifically are effective in the treatment of leukemia in children and in the management of hemolytic anaemia and hemorrhagic complications of thrombocytopenia that mostly occur in malignant lymphomas and chronic lymphocitic leukemia. Acute lymphoblastic leukemias in children are better treated with corticosteroids rather than antimetabolities and remission take place more rapidly. The **hormones** have been beneficial in breast cancer and other carcinomas although palliative effects are of short duration.

A few important compounds are discussed here, namely : **Megestrol ; Mitotane and Testolactone ;**

A. *Megestrol* BAN, ; *Megestrol Acetate* USAN :



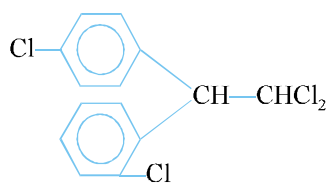
17-(Acetoxy-6-methyl-pregna-4, 6-diene-3, 20-dione, Megesterol Acetate BP (1973) :

Ovarid(R) (Glaxo) ; Megestat(R) (Bristol) ; Megace(R) (Mead-Johnson) ;

It is indicated for the palliative treatment of endometrial carcinoma and advanced breast cancer when other methods of medication are not effective.

Dose. *Usual, 160 mg/day in four equal doses in breast cancer, ; 40-320 mg/day in equal divided doses in endometrial cancer.*

B. *Mitotane* USAN ;



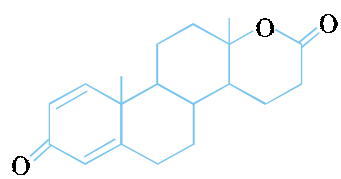
1, 1-Dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl) ethane ; *o, p*-DDD ; USP ;

Lysodren(R) (Bristol) ;

It is indicated mainly for the treatment of inoperable adrenal cortical carcinoma.

Dose. *Usual, 8-10 g per day, divided into 3 or 4 equal doses.*

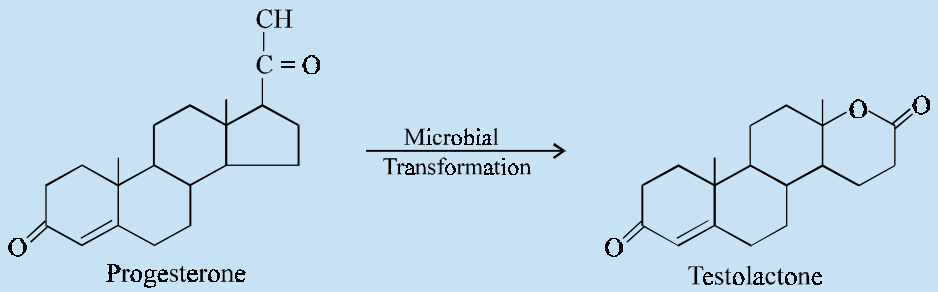
C. *Testolactone* USAN ;



1-Dehydrotestololactone USP ;

Teslac(R) (Squibb) ;

Synthesis



It may be prepared by microbial transformation of progesterone.

It is invariably employed in the palliative treatment of advanced breast cancer in postmenopausal women.

Dose. *Usual, 250 mg 4 times per day by mouth or 100 mg intramuscularly thrice weekly.*

2.6.1. Mechanism of Action

The **mechanism of action** of some drug substances discussed under section 2.6 shall be treated individually in the section that follows :

2.6.1.1. Magestrol Acetate

It is well established that not only normal, but also well-differentiated neoplastic target cells to possess a plethora of strategically located '**hormone receptors** ; and eventually they bank upon the hormones for stimulation.* Importantly, the rather comparatively less differentiated neoplastic cells invariably become independent of the ensuing '**hormonal control**' and thereby lose their specific receptors eventually. Evidently, a few malignant tumours are solely hormone dependent and responsive to hormone-based therapy, on the contrary others are independent and naturally altogether unresponsive. Hence, magestrol acetate exert its action on hormone dependent tumours *e.g.*, endometrial carcinoma and breast cancer.

2.6.1.2. Mitotane

The '**drug**' is found to be toxic to the adrenal cortex and, therefore, it is exclusively indicated for the treatment of *inoperable adrenal cortical carcinoma.* It is metabolized in the liver. Approximately 40% of a single oral dose gets absorbed ; whereas, the '**drug**' gets excreted in urine in the form of an **unidentified metabolite** ranging between 10-25%, and almost 60% is excreted absolutely unchanged in faeces. The remainder of the '**drug**' gets stored in the adipose tissues *in vivo.*

2.6.1.3. Testolactone

The '**drug**' obtained *via* microbial transformation of progesterone** is found to be devoid of any androgenic activity in the usual recommened dosage regimens.

2.7. Immunotherapy

It is now an established fact that the human body continually produces cells having neoplastic potential which are destroyed by our immune surveillance system. The very formation of tumours suggests

* Fried J *et. al. J. Am. Chem. Soc.* **75 :** 5764, 1953.

that this system is impaired. In other words, suppression of body's immune system by these agents easily results to development of serious viral, bacterial and fungal infections.

Biochemical modulation of the action of some of the **antineoplastic agents** has more or less provided a means of improving their specificity for tumour cells. **Biological modifiers specific antibodies** such as **interferons**, **interleukins** and agents that might affect or arrest cancerous growth by inducing terminal differentiation have been also applied but there exists only limited evidence till date that these agents can affect widely disseminated cancers, It may, however, be ascertained confidently that treatment with biological response-modifiers amalgamated with improved form of chemotherapy will ultimately lead to significant enhancement both in the arrest and even cure of wider spectrum of neoplasma.

One important member of this group is discussed here, namely : **Interferon Alfa-2*a* recombinant**.

A. *Interferon Alfa-2a, Recombinant*

It is prepared on a large scale from a strain of *E. coli* having essentially a plasmid produced by the technique of genetic engineering, otherwise known as recombinant DNA technology, consisting of an interferon alfa-2*a* gene from human leukocytes.

It is employed in subjects above the age of 18 years for the treatment of hairy cell leukemia.

Dose. *In hairy cell leukemia the dose of interferon alfa-2a and alfa-nl is 3 million units daily by deep intramuscular or subcutaneous injection until there is improvement or for up to 24 weeks, then redcued to a maintenance dose of 3 million units 3 times a week.*

2.7.1. Mechanism of Action

The **mechanism of action** of the **interferon alfa-2*a*, recombinant** is discussed as under :

2.7.1.1. Interferon Alfa-2a, Recombinant

The **'drug'** enhances class I histocompatibility molecules on lymphocytes, increases the production of **ILs-1 and -2**,* regulates antibody responses, and above all enhances **NK cell**** activity. Besides, it also inhibits cancerous tumour-cell growth by virtue of its inherent ability to inhibit protein anabolism (synthesis) *in vivo*. The '**drug**' is antiproliferative ; and, therefore, may also serve as immunosuppressive. It is, however, pertinent to state here that the prevalent action of the **'drug'** upon the **NK cells** is believed to be the most important and critical factor for its prevailing **antineoplastic profile.**

The '**drug**' also exhibits antiviral activity, specifically against the RNA viruses. Furthermore, it appreciably enhances the strategic targetting of monoclonal antibody-tethered cytotoxic drugs to the corresponding malignant cells.

The '**drug**' is not absorbed when administered through mouth. However, by IV route it exclusively disappears within a span of 4 hours, but by the IM or sub-cutaneous route disappearance gets prolonged to 6-7 hours.

Probable Questions for B. Pharm. Examinations

1. What is a neoplasm ? What are the causations of neoplasm ? Give the structure, name and uses of at least **three** potent drugs employed as antineoplastic agents belonging to :

(*a*) Natural plant source

(*b*) Synthetic drugs.

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* Mediate most of the toxic and therapeutic effects.

**Natural killer cells.